BLOOD-VESSEL SURGERY AND ITS APPLICATIONS

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BLOOD-VESSEL SURGERY AND ITS APPLICATIONS

BY

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GENERAL EDITORS' PREFACE

The Editors hope to issue in this series of International Medical Monographs contributions to the domain of the Medical Sciences on subjects of immediate interest, made by first-hand authorities who have been engaged in extending the confines of knowledge. Readers who seek to follow the rapid progress made in some new phase of investigation will find herein accurate information acquired from the consultation of the leading authorities of Europe and America, and illuminated by the researches and considered opinions of the authors.

Amidst the press and rush of modern research, and the multitude of papers published in many tongues, it is necessary to find men of proved merit and ripe experience, who will winnow the wheat from the chaff, and give us the present knowledge of their own subjects in a duly balanced, concise, and accurate form.

Among the great advances in medical science which have been made in the first decade of the twentieth century, one of the most amazing is set forth by Professor Guthrie in his admirable account of Blood-Vessel Surgery. Co-operating with Dr. Carrel, he became a pioneer in the successful development of the new technique, and by its means carried to a successful issue some most extraordinary experiments on the transplantation of vessels and organs, culminating in the grafting of both kidneys with segments

of aorta and vena cava from one cat to another. From such an operation cats recover quickly, and the grafted kidneys for many days secrete a urine normal in amount and composition. But this state of good health does not continue, and after some three weeks the animal dies from some subtle impairment of renal metabolism, brought about by the heterogeneous nature of the graft. After a graft of its own kidney has been made, a cat has lived in unimpaired health for two years! Hereby we see the characteristics of each organ stamped with an individuality which prevents exchange even with another taken from the same species.

Professor Guthrie tells us that the successful method of carrying out blood-vessel surgery was initiated in 1899 by Dörfler, who employed fine round needles, fine silk, and continuous sutures which embraced all the coats of the vessel.

He gives the surgeon a full and detailed account of the exact methods of carrying out the operations of repair and union of blood-vessels, every step in the procedures being illustrated by an admirable series of figures. The results obtained so far show that completely divided vessels can be sutured with almost uniform success, the circulation continuing unimpaired through the united vessels. Carrel obtained success when he transplanted heterografts—*e.g.*, segments of dogs' vessels into cats—and even after keeping the grafts for many days in an ice-chest!

Guthrie has successfully engrafted segments of the abdominal aorta of a cat and of a rabbit between the ends of the divided common carotid of dogs, and lastly—more wonderful than all—has engrafted into the carotid of another dog a segment of dog's vena cava which had been preserved for two months in formalin and then treated successively with dilute ammonia, alcohol, and paraffin oil.

He gives us a picture of a fat and smiling pug-dog, in which the carotid artery was pulsating three years after the introduction of

the dead and hardened graft. Such grafts act as a scaffolding for the ingrowth of fibrous tissue and the spread of the intima from the living vessel. Meanwhile the smooth inner lining of the dead graft adequately conducts the circulating blood.

The experiments of Carrel and Guthrie bring within the realms of possibility, under favourable conditions of locality, the removal of an aneurysm and the restoration of vascular continuity by the insertion of a sterilized graft taken from the post-mortem room.

The physiological application of the methods of blood-vessel surgery quickly followed on their perfection. Not only kidney, but thyroid autografts have proved adequate in function. It is possible for the surgeon to locate such organs in new places—*e.g.*, the kidney can be placed in the neck and functionate when supplied by the carotid artery. So far only the autografts of organs have continued to carry on their function for long periods of time. Heterografts succeed at first, but inevitably fail after the first few weeks. This is the disappointing but unanimous conclusion of the experimentors. Thus there is, at present, no temptation for the enthusiastic surgeon to try and graft one lobe of the thyroid or a kidney taken from a healthy donor. The poor man will not be tempted to exchange one of his sound kidneys for so much hard cash. It would be interesting to see whether a graft from one of a litter to another would succeed.

The limb of an animal has been removed and engrafted, and the limb has survived for many days; no one, however, has succeeded yet in obtaining a return of function in the limb. The cripple cannot yet hope to have grafted on him another leg taken from some unfortunate who had just been accidentally killed.

It is interesting to note that the experimental results obtained do not lend any support to the view that deficiency of an organ is necessary for the survival of a graft of that organ.

In carrying out autografts, Professor Guthrie has shown that perfusion of the grafts with physiological salt solution is a disadvantage. Kidneys engrafted without perfusion give much better results. He has found human hairs form excellent material for stitching blood-vessels together. Such ligatures are easily obtained and prepared.

His most astonishing results have been obtained by the successful grafting of hens' ovaries (without vascular anastomosis). The grafts have taken and lived, and the hens have laid eggs from which chicks have been hatched. Pure black Leghorn hens have been grafted with ovaries taken from pure white Leghorns, and *vice versa*, and the hens have been covered, some by cocks of their own hue and others by cocks of opposite colour. Spotted chickens have resulted, while all the controls have bred true. The evidence is in favour, then, of foster-mother, or *soma*, influence.

Professor Guthrie discusses the results in relation with "graft-hybrids" and Darwin's views of the same. Graft-hybrids are produced by joining two young stems or two pieces of potato tuber together, each piece being taken from a different variety. The plants thus raised yield numbers of new forms of tubers, many of which appear to be of intermediate character.

It is a question whether "soma influence" really was at work in Guthrie's experiments, or the alteration of nutritional conditions increased the number of variations arising spontaneously in the egg-cells. Those who are interested in the problems of heredity will find much of interest in these experiments.

In the last part of the book Professor Guthrie discusses Resuscitation and Shock, and gives an admirable account of the scientific evidence on which is established the period of survival of the organs after a temporary cessation of the circulation. The author rightly attributes traumatic or psychical shock to a general inhibitory

state, and is wise in his suggestions as to treatment of this condition.

Professor Guthrie has given us a most suggestive and valuable work, full of material of immediate practical interest to the surgeon, the physiologist, and to him who studies the problems of heredity.

LEONARD HILL.
WILLIAM BULLOCH.

December, 1911.

AUTHOR'S PREFACE

No attempt has been made to cover exhaustively all divisions of the subject of blood-vessel surgery and its applications. The scope of treatment conforms to the inclination of the writer. Naturally, therefore, he has been guided largely by his familiarity with the matters treated, from his experience and knowledge as a physiological investigator and teacher; and for this reason it may seem that undue attention is given to certain divisions and too little to others. But in this way it was believed that the scope of the work would more certainly remain within the field of his special qualification.

In general, historical considerations, or the names of investigators in this or any other scientific field, are of secondary importance, for "knowledge has value in proportion to the benefit it confers on the human race"—in the present instance on surgical patients it would seem, and not on surgeons or investigators, much less on mere compilers and writers. Facts are valuable in the degree that they lead to the prevention, alleviation, or banishment of human suffering. The association of Jenner's name with vaccination added nothing to the efficacy of the latter. Simple expression of the truth is the only style consistent with science itself. And the unsuppressed, purely human or sentimental trait that results in modern scientific writings being crowded with the names of men in an unscientific and sometimes what presents the appearance of

a vainglorious manner, is deplorable. The writer regrets his weakness in being conventional rather than sincere in this respect.

The work is intended to give the facts of blood-vessel surgery and its applications, but no doubt errors occur. As knowledge advances, statements that now seem warranted will cease to hold. But this, it would seem, is inevitable. In so far as seemed desirable, references have been given for the benefit of the reader desiring to investigate any part of the subject in the literature. The portion of the work devoted to discussion is of secondary importance or value, as it represents only the writer's views based on his knowledge and experience. It is "by theoretical considerations that our knowledge is (sometimes) advanced." So it is possible that this portion of the work may aid in the discovery of new facts, or further application of the facts, which is the sole excuse for its inclusion.

My thanks are due to a number of investigators who have kindly granted permission to use their materials freely, and a number of editors and publishers for similar permission in the use of copyrighted materials.

In conclusion, I desire to acknowledge my indebtedness to Professor Clyde Brooks, Dr. A. H. Ryan, Miss Frances Virginia Guthrie, and Mr. William Irving of my staff, for much aid in the preparation of the manuscript, in the correction of the proof-sheets, and so forth.

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BLOOD-VESSEL SURGERY
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PART I

CHAPTER I

HISTORY OF BLOOD-VESSEL SURGERY

Repair of Simple Vascular Injuries.

UNTIL 1899 but a relatively small number of arteries had been repaired successfully by direct suture. It is recorded that in 1759 Hallowell closed a wound in a brachial artery by thrusting a pin through the margins of the wound and tying a thread about it. It is usually considered that this operation was successful, as the radial pulse remained quite strong. But a few years later Asman tested the method on dogs ; none of his operations were successful. In 1881 Glück successfully repaired a wound in an artery by means of small ivory clamps. In 1889 Jassinowski proved that arteries could be successfully repaired by suture. He used fine curved needles and fine silk, and made interrupted (buttonhole) stitches placed close together. He endeavoured to avoid penetrating the intima. Out of twenty-six experiments, twenty-two were successful, and some of the specimens were not taken for more than three months after the operation. The next year Burci confirmed the results of Jassinowski. Only, in addition to using fine round needles and fine silk, he made continuous stitches. In 1897 Murphy reported successful results from having sutured vessels with fine silk. At the same time, and little later, Silberberg successfully sutured arteries, including the abdominal aorta. For the most part he employed a continuous suture of the finest silk, which was placed with Hagedorn intestinal needles. He did not lay much stress upon the point as to whether or not the intima should be included in the stitch. Previous to this time, most investigators emphasized the importance of confining the stitch to the outer vascular coats.

In 1899 Dörfler published the essential features of the method now so universally and successfully employed, the essential features being the employment of *fine round needles and fine silk, and continuous sutures embracing all of the coats of the vessel.* Of sixteen experiments, twelve were successful. He concluded that fine cambric needles and silk thread would give excellent results in suturing blood-vessels. And from the observation that the presence of an aseptic silk thread in the lumen of a vessel did not necessarily lead to changes which might interfere with the patency of the lumen, he concluded that the penetration of the intima was not contraindicated. In fact, he recommended that all coats be included in the continuous suture. The method is also adapted to repairing veins.

Union of Vessels.

The first permanent union of two blood-vessels was accomplished in 1879 by Eck, a Russian surgeon. This renowned pioneer in the

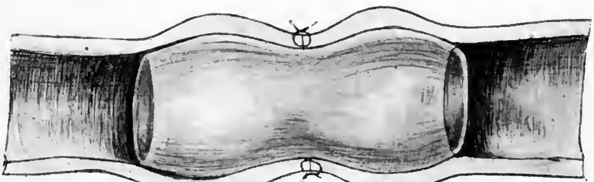

FIG. 1.—ABBE'S METHOD OF END-TO-END UNION OF BLOOD-VESSELS BY MEANS OF THIN GLASS TUBES.

field of vascular union successfully established a lateral communication between the portal vein and the vena cava. Thus, not only

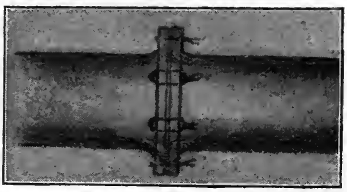

FIG. 2.—BRIAU AND JABOULAY'S METHOD OF DIRECT END-TO-END UNION OF BLOOD-VESSELS.

was the way opened for exploration, but the application of this operation by physiologists such as Minkowski, Pavlov, and others,

in the study of metabolism has yielded brilliant and far-reaching results.

V. Hirsch, in 1881, is accredited with having successfully sutured divided veins of dogs. In 1896 Briau and Jaboulay successfully united the ends of a divided carotid artery of a donkey by means

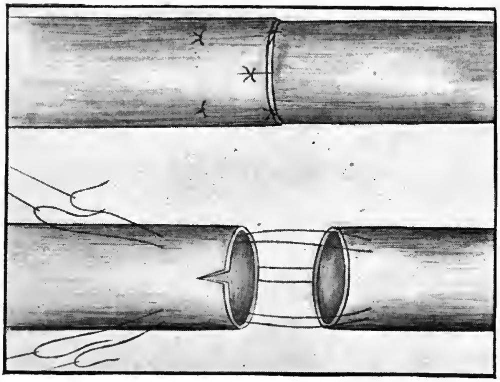

FIG. 3.—MURPHY'S EARLIER METHOD OF VASCULAR ANASTOMOSIS.

of U-shaped sutures so placed as to produce eversion of the edges of the walls and approximation of the intimas. Murphy, in 1897, published an invagination method carried out by means of silk ligatures, by which he successfully united the ends of divided arteries. Also he practised such anastomoses by means of con-

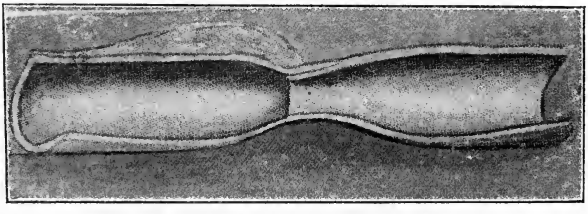

FIG. 4.—ENDS OF A BLOOD-VESSEL UNITED BY MURPHY'S INVAGINATION METHOD (*Medical Record*, 1897, 14), SHOWING THE USUAL CONTRACTION AT THE SEAT OF APPROXIMATION.

tinuous and interrupted sutures, one such operation out of five being successful. In 1900 Payr described a method of arterial anastomosis by invagination carried out by means of magnesium rings somewhat similar to the ivory clamps recommended by Nitze in 1897. Payr claimed to have used the method successfully. In

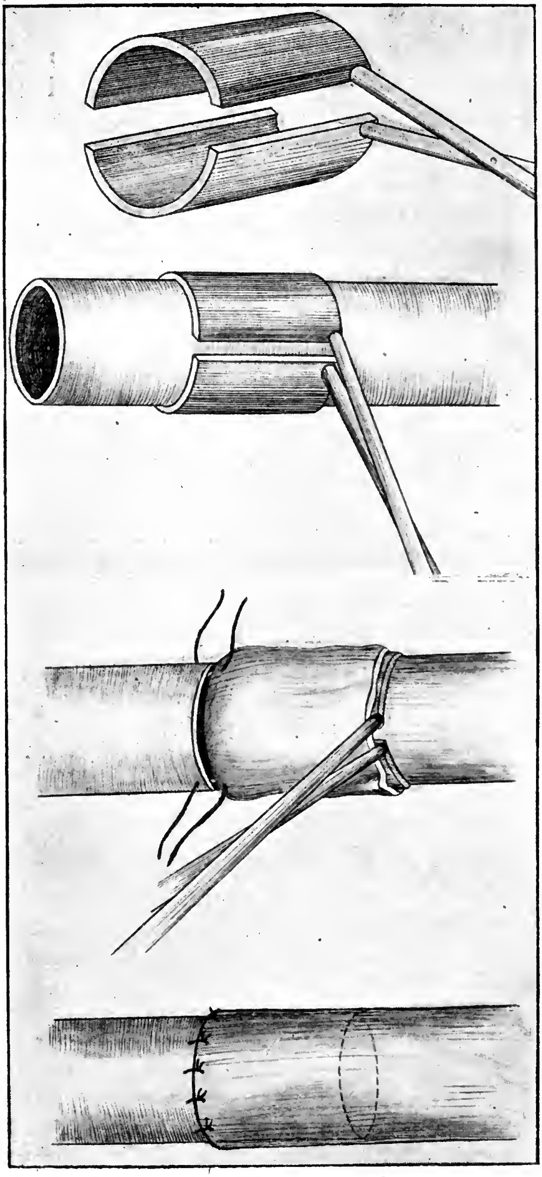

FIG. 5.—MURPHY'S MORE RECENT METHOD OF END-TO-END ANASTOMOSIS OF BLOOD-VESSELS BY INVAGINATION.

1901 Bouglé reported a successful arterial anastomosis by means of an invagination method, and also a successful result by simple end-to-end union by interrupted sutures. Fifteen days after the

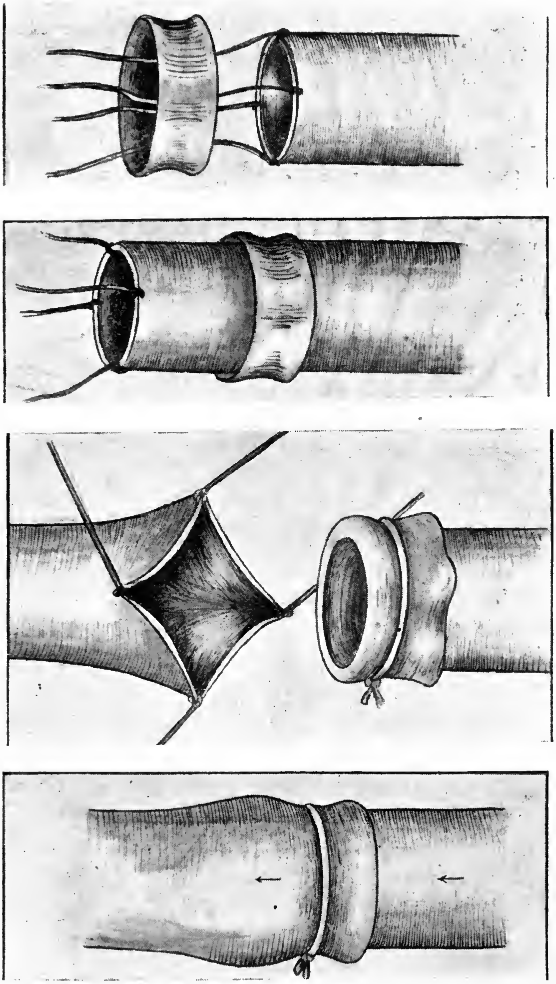

FIG. 6.—PAYR'S METHOD OF END-TO-END ANASTOMOSIS OF BLOOD-VESSELS BY MEANS OF ABSORBABLE RINGS.

operation both the vessels were patent and the intimas were smooth. In the same year Clermont reunited the ends of a divided inferior vena cava by means of a continuous fine silk suture, and a month later the lumen of the vessel at the point of operation was smooth

and unobstructed. In 1902 Tomaselli reported the results of eleven arterial anastomoses. He used interrupted sutures of fine silk. In seven of the cases successful results were obtained. In 1902 Salvia reported that out of sixteen anastomoses by Murphy's method two remained patent, though the lumen was narrowed. But six of these wounds showed infection. In the same year Berard and Carrel began the study of end-to-end arterio-venous anastomoses. The suture method they used was essentially like that of Dörfler, consisting in the placing of continuous sutures of fine silk by means of fine round needles. These investigators

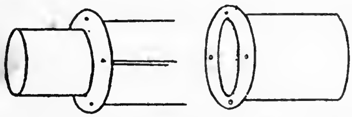

FIG. 7.—PAYR'S MODIFIED METHOD OF VASCULAR ANASTOMOSIS. (STICH.)

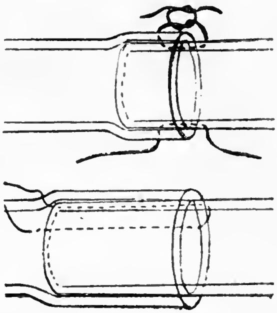

FIG. 8.—BOULGÉ'S METHOD OF VASCULAR ANASTOMOSIS.

differed from Dörfler in that they endeavoured to avoid penetrating the intima. The femoral artery and the saphenous vein of a large dog were exposed in Scarpa's triangle, and the central end of the artery was united to the peripheral end of the vein. The anastomosis adequately withstood the blood-pressure, but no physiological results were observed, as the animal died from infection two days after the operation.

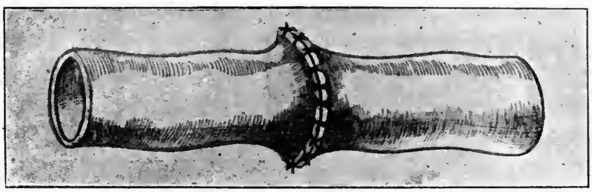

FIG. 9.—SALAMONI'S METHOD OF END-TO-END UNION OF BLOOD-VESSELS.

In another case the vessel was found to be occluded by a fibrous clot eight days after the operation. In an experiment by Carrel and Morel the peripheral end of a divided jugular vein was united to the central end of a divided carotid artery. This specimen was not examined directly, but several weeks after the operation the external jugular vein pulsated like an artery. In 1903

Jensen reunited the ends of divided veins by means of continuous sutures, which penetrated the intima, and of seven such operations four were successful. In the same year Höpfner reported the results of extensive studies on vascular anastomoses. He employed a circular suture of the vessels, and four of six arteries thus united were successful. He also reported having removed and success-

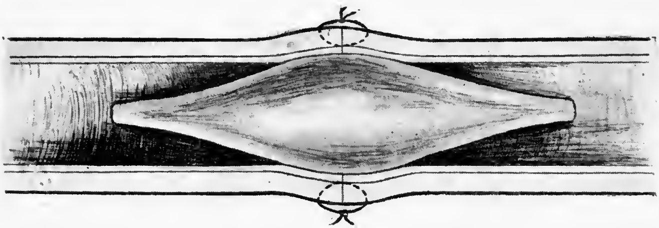

FIG. 10.—DE GAETANO'S METHOD OF END-TO-END UNION OF BLOOD-VESSELS. (Keen's "Surgery," 1909, v. 133.)

fully replaced a segment of common carotid artery by means of Payr's magnesium ring method. One of the two operations of this description was proved to be successful by direct examination after one month. In another experiment a segment of a dog's common carotid artery, more than an inch in length, was interposed between and anastomosed to the ends of one of the femoral arteries from which a similar segment had been removed, and the latter segment was interposed between the ends of the divided carotid artery. Examination two months later revealed smooth intimas and but little constriction, or, in other words, excellent results. He also successfully engrafted a segment of femoral artery of an animal between the ends of a carotid artery of another individual from which a segment had been removed. Floresco early in 1905 reported the results of numerous end-to-end anastomoses of arteries and veins which were performed in engrafting kidneys in dogs. The experiments were begun in 1902. So far as vascular anastomosis was concerned, he seems to have been successful.

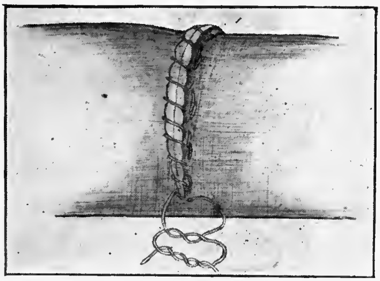

FIG. 11.—DORRANCE'S METHOD OF SUTURING BLOOD-VESSELS.

In 1905 Carrel and the writer conjointly began experimenting with the anastomoses of blood-vessels in the Hull Physiological

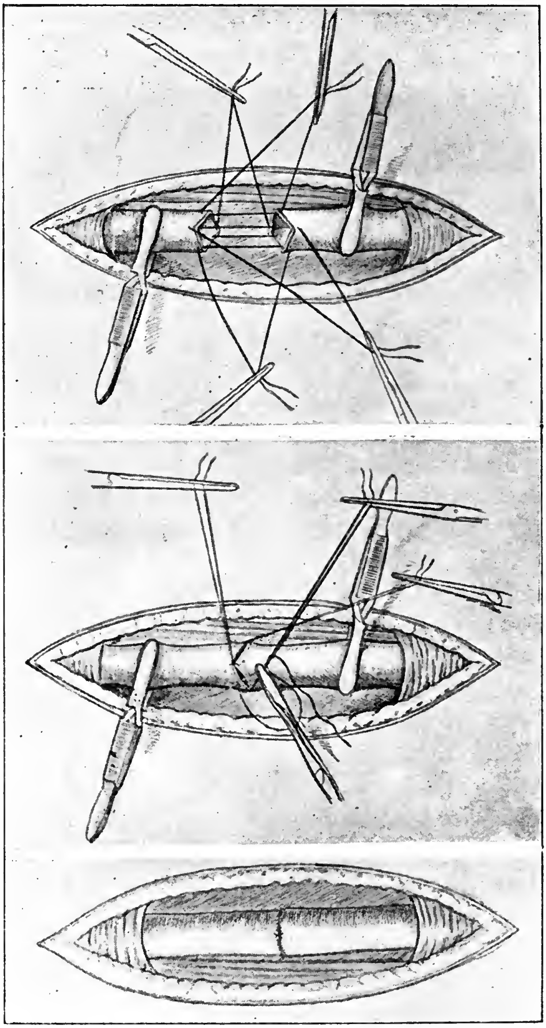

Fig. 12.—Frouin's Method of End-to-End Vascular Anastomosis. (*Presse Médicale*, 1908. *Cf.* p. 232.)

Laboratory of the University of Chicago, "with the view, among others, of making a complete study of the transplantations of veins. Several series of experiments were undertaken in order to study

the results of the uniterminal and biterminal venous transplantations, and they were thoroughly successful." The technique previously studied by Berard and Carrel and by Carrel and Morel in 1902 was first tried, but very soon the endeavour to avoid penetrating the intima was discontinued, and its inclusion in the stitches as recommended by Dörfler was practised. Other modifications were developed, until "finally we developed a technique which is equally well adapted for arterio-arterial, veno-venous, or arterio-venous anastomoses, and which yields uniformly successful results. This new technique has been used since 1905. Numerous arterio-venous anastomoses and transplantations of veins have been successfully performed." Especially noteworthy of these experiments is the constancy and perfection of the results of the vascular anastomoses, whether between arteries or between veins or between arteries and veins; the proof that the circulation through a vein may be reversed; the demonstration that a segment of vein may be successfully sutured to the ends of a divided artery to restore the continuity of the arterial lumen; that an opening in an artery may be successfully closed by a patch of peritoneum; and certain information regarding the engrafting of tissues with vascular anastomoses (which will be considered in the following division of this review). Watts, in 1906, repeated many of our experiments with confirmatory results

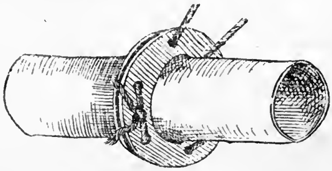

FIG. 13.—ANASTOMOSIS OF BLOOD-VESSELS BY MEANS OF METAL FLANGES. (LESPINASSE, FISHER, AND EISENSTAEDT.)

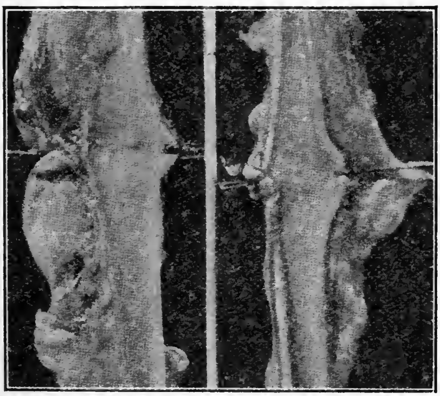

FIG. 14.—RESULTS OF ARTERIAL ANASTOMOSES BY MEANS OF METAL FLANGES. (LESPINASSE, FISHER, AND EISENSTAEDT.)

Common carotid operation. Dog killed 112 days later. The arteries were dissected out, and demonstrated to be pulsating. They were clamped and cut distal to the anastomosis. In each instance the blood spurted. The vessels were then split open and mounted. Age of operation, 112 days; magnesium practically gone; few small pieces still present; vessel smooth; no constriction.

(for figures, see Chapter IV.). In reviewing his results, he states "that of thirty-one experiments upon the vessels of the neck, twenty-eight were successful. . . . Also, that the results show conclusively that completely divided vessels can be sutured with a most uniform success, . . ." and that "the intima can be included in the suture with impunity, the application of the suture being thus greatly facilitated." Since that time the results have been reconfirmed by many other experimenters. In 1907 both Carrel and the writer reported successful results from repairing divided blood-vessels with segments of blood-vessels from different species of animals. Carrel transplanted segments of dogs' arteries which had been kept for some time in an ice-box into cats, two of five such operations being successful. The writer successfully engrafted a segment of the abdominal aorta of a cat and of a rabbit between the ends of divided common carotid arteries of dogs. In 1908 the writer successfully engrafted a segment of dog's vena cava which had been preserved for two months in 2·5 per cent. formalin solution, and then treated with dilute ammonia water, concentrated alcohol, and paraffin oil, between the ends of a divided common carotid artery of a dog. Carrel held that the tissue elements of segments of blood-vessels kept on ice for some time before being engrafted survived. But the writer, on the bases of the histological study of a segment of rabbit's aorta engrafted between the ends of a divided common carotid artery of a dog, and the successful engrafting of a formaldehyde-fixed segment of dog's vena cava between the ends of a divided common carotid artery of a dog, concluded that the elements of such engrafted segments to meet the vascular requirements need not, and probably do not, survive, but that for a time they may mechanically perform the circulatory function and serve as a bridge for the ingrowth of the other cells, and themselves ultimately suffer degenerative, disintegrative, and absorptive changes. For the segment of rabbit's aorta on dog's carotid was adequately transmitting the arterial blood eight months after the operation. Yet the gross appearance of the segment was vastly altered, being greatly enlarged, the walls thickened and hardened (calcified) (see p. 93 for detailed account). And, though performing an adequate circulatory function, the tissue elements of the formaldehyde fixed and absolute alcohol treated segment could not be considered to have survived.*

In 1910, with F. V. Guthrie, the writer announced that divided

* *Cf.* Carrel, *Jr. Exp. Med.*, 1911, xiv. 126.

blood-vessels could be successfully sutured together with human hair, the stitches being of the continuous variety and penetrating the intima. The chief value of this result, perhaps, is the knowledge that a suture material with which successful vascular operations may be performed is widely distributed. And, since it is not easy in all places to quickly obtain suitable thread for such suturing, it is by no means improbable that the fact that hair may be used may later be of practical value.

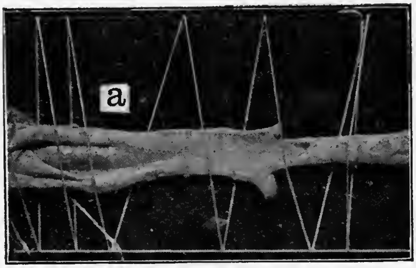

Fig. 15.—Central End of Left Common Carotid Artery Anastomosed to the Peripheral End of the Left Internal Jugular Vein with Human Hair.

Results of Vascular Suture in Man.

Up to the beginning of the last decade, though not absent, mention of successful vascular suture in man was rarely entered in the literature. And at least the majority of such cases reported belonged to the doubtful class, to be presently discussed, as regards conclusiveness of evidence of success.

Until 1900, according to Dörfler, but a very small number of arteries in man (nine) had been repaired successfully by direct suture. At this time two cases operated upon by Garré were added to the list. One of these consisted in the suture of one of the common carotid arteries on the removal of a tumour. The patient recovered, but died a few months later. No post-mortem examination was made. In the other case the brachial artery was sutured, and, though diminished, a pulsation of the radial and ulnar arteries persisted. The conclusion was drawn that both operations were successful. Other similar cases might be cited from the literature, but the two given are fairly representative, and will therefore serve, together with what follows, to illustrate the fallacy of drawing definite conclusions from such cases. But first it must be stated that it is assumed that in such instances the term "success" is employed to mean that the lumen of the vessel remained patent at the point of operation—at least, until primary healing of the vessel was complete.

In analyzing the observations presented in the report of the two cases, it is observed that in the case of the operation on the common carotid artery that no symptoms attributable to occlusion were

seen. Now it is known that in man ligation of one of these arteries is not necessarily followed by symptoms of circulatory deficiency. So it must be concluded that the observation reported proves nothing so far as preservation of patency of the arterial lumen is concerned.

The second case, which involved suture of the brachial artery, likewise proves nothing in this respect. It is true that the continuation of the radial and ulnar pulse strongly indicates at least a temporary preservation of the arterial lumen, for if such a vessel be ligated, pulsations in the distal trunks ordinarily for a time disappear or become impalpable. But, as Guthrie pointed out in 1830, as the extent of collateral circulation by way of anastomotic connections between different portions of the vascular trunks varies considerably, it is possible that in a case presenting unusually free connections of this character, ligation of the main arterial trunk would not diminish the circulation to the point of extinction of a detectable pulsation in the distal arteries. Also, it is known that the gradual occlusion of an arterial trunk is accompanied by the rapid development in size of anastomotic channels, so that at the moment the lumen of the vessel becomes completely closed, the collateral channels may be sufficiently large to transmit the pulse-wave. And for these reasons the observation of a pulse in the distal arteries is no proof of the success of the vascular suture. It may be remarked that Matas, by applying this principle, has evolved a method of causing ablation of aneurismal sacs.

Guthrie legitimately concluded from his numerous observations and the observations of others that gangrene, though not unknown, by no means necessarily follows ligation of the main brachial or femoral vascular trunks. So the absence of this dread complication after suture of such vessels with the view of permanent preservation of patency as direct circulatory channels is no proof of successful execution of the laudable intention.

As discussed more freely elsewhere (p. 69), even the abdominal aorta may be permanently occluded posterior to the renal vessels with at most but temporary clinical evidence of circulatory derangement in the posterior portion of the trunk and extremities. So the report of successful suture of such vessels cannot be accepted on evidence other than that furnished by direct inspection of the vessel at the point of operation. In 1902, according to Schmitz, twenty-one successful arterial sutures in man had been reported; and in 1903, according to Dörfler, the number had been raised to

thirty. In 1910 Stich stated that such successful operations numbered more than a hundred.

For some reason, until recently, fine gut and needles of the ordinary surgical type were employed for suturing blood-vessels. This, I believe, may be traced back to pre-anti- and pre-aseptic days, when the date upon which "the ligature came away" after a vessel was ligatured was almost invariably recorded. During this period large ligatures were employed—indeed, tapes were sometimes used. Guthrie was one of the first to recognize the advantage of a thin "well-waxed" ligature. But this type of ligature also "came away" by sloughing. So what must have been the condition of the wounds when tapes were employed—virtual setons!

But knowing of this state of affairs, and contrasting it with the clean healing of wounds, and the safety of deep-placed absorbable sutures after the dawn of modern surgical methods, it is perhaps not so surprising after all that even in comparatively recent writings is to be found the recommendation of gut as vascular suture material. Another curious angle of the subject is seen in the fact that for years prior to development of a successful suture method of vascular anastomosis almost the identical character of materials and method was employed for intestinal suture, the differences being not fundamental, but chiefly in size of threads and needles.

Results of Transplantation of Tissues by Vascular Suture.

In 1903 Höpfner, in v. Bergmann's clinic, reported the results of amputation and retransplantation of the hind-limb of a dog with reunion of the blood-vessels by Payr's magnesium ring method. Good results were obtained for eleven days, at which time the animal was killed with chloroform. In 1905 Carrel and the writer repeated this experiment, using the suture method for anastomosis of the blood-vessels. Other similar experiments have since been performed, but the results achieved have advanced our knowledge but little beyond the stage attained from the experiments reported by Höpfner—that is to say, no one has as yet observed the return of function in the replanted or transplanted limb.

Ullmann, in 1902, removed and transplanted a dog's kidney into the cervical region, uniting the renal and carotid artery and the renal and external jugular vein by Payr's method. The kidney secreted for a time after the operation. In the same year v. Decastello performed similar experiments. In a case where he engrafted a dog's

kidney into another dog over a litre of urine was secreted by the engrafted organ. But, owing to a hæmorrhage, the animal lived a little less than two days. Floresco, in 1905, reported the results of numerous renal engrafting experiments which he began in 1902. He recommended circular suture of the blood-vessels, and that the organ be engrafted into the abdominal cavity. One of his animals lived for more than a month after one of its kidneys was removed and replaced by a kidney from another dog (see p. 230). But he did not present proof of permanent functional survival of an engrafted kidney. He collected and analyzed urine from engrafted kidneys; also he studied the structure of such kidneys. He tested various methods of preventing coagulation in the vessels of kidneys during the engrafting operation, as the injection of salt solutions to displace the blood, and the injection of peptone solutions and solutions of leech extract into the general circulation prior to the operation, in order to decrease the coagulability of the blood. He seemed to consider that the injection of salt solution into the kidneys was not, perhaps, a harmless procedure.

Carrel and the writer, in 1905, performing similar renal transplantations, obtained similar results. After devising a new method, which we termed "transplantation in mass," by means of which it was possible to transplant both kidneys by removing and engrafting segments of the aorta and vena cava bearing the renal vessels, they succeeded in keeping animals alive with wholly engrafted renal tissue for a longer time than had been previously reported. Dogs and cats were used in the experiments. Some animals lived for weeks after their own kidneys had been removed and replaced by kidneys from other animals of the same species. Since that time Carrel and several other experimenters have succeeded in keeping an animal alive even for months with its own renal tissue after it had been removed and re-implanted. Owing to the unsatisfactory nature of the results obtained with Carrel, especially as regards lack of permanency, the writer early came to the conclusion that the perfusion of the kidneys with salt solution, which was practised in the experiments, in itself was not above suspicion of being a harmful agent. Therefore, a series of experiments to test this point were carried out by him, and the results proved that salt solution had such an action (1907-08). A large number of cats were experimented upon by temporarily clamping off a segment of the aorta bearing the mouths of the renal arteries, and displacing the blood from the kidneys with salt solutions introduced into the aortic

segment by means of a trocar thrust into the lumen. The majority of the animals sooner or later developed pronounced symptoms of renal insufficiency and died, even though the total period of occlusion of the renal circulation was considerably less than the time required for the transplantation of a kidney or kidneys. Also the experiments demonstrated that mere temporary shutting off of the circulation was a much less dangerous procedure than when accompanied with perfusion. Therefore, it was suggested that kidneys engrafted without perfusion might give better results than had been the rule in the past. But, owing to removal to another institution, the experiments suffered an interruption.

Borst and Enderlin, in 1909, engrafted one of a dog's kidneys on to the splenic vessels, and it is stated that the animal lived for one hundred days after ablation of its remaining normal kidney. But they, in agreement with all others, have been unable to obtain a long period of survival of an animal with a kidney or kidneys from another animal, even though the animals were closely related. Carrel, in 1909, claimed to have succeeded in obtaining a successful result after removing and replacing one of a dog's kidneys, and then after fifteen days by a second operation removing the unmolested kidney.

Lespinasse has reported similar results—that is, in experiments on dogs when one kidney was removed and the artery of the other divided and the ends reunited. All but one of the animals died. In this animal the blood-supply in the kidney was shut off for approximately one hour. But in another series of experiments one renal artery was cut and the ends reunited, in one experiment the artery being occluded for approximately fifty minutes. In these dogs, by a second operation ten days later, the unoperated kidneys were removed, and none of the animals died.

Zaaiger has reported having observed a dog to survive for two years upon auto-engrafted renal tissue—the longest result hitherto reported. In 1910, Villard and Tavernier reported results they obtained by engrafting kidneys without perfusion which are very encouraging. In one experiment after fifty-six days the urine from the engrafted kidney contained 2·8 per cent. urea, and was albumin free. Another such kidney examined sixty-eight days after the operation, except for a slight nephrosis and thickening of the capsule, was macroscopically normal. But no one has as yet succeeded in keeping an animal alive for more than a few weeks with engrafted renal tissue from another, though even a closely related individual,

after removal of both of its own kidneys. So the operation at the present time is only of experimental interest.

In 1905 Carrel and the writer replanted a lobe of the thyroid gland in a dog with vascular anastomoses with success as regards preservation of structure (p. 247). But the gland was not put to the functional test. In 1908 Capelle, in reporting some experiments performed at Garré's clinic, stated that the thyroid had been successfully replanted into a dog's neck. The dog developed normally for 245 days after the operation, at which time the thyroid was removed and the animal rapidly succumbed to typical post-thyroidectomy tetany. Thus we have evidence of functional survival of the engrafted thyroid.

This concludes the list of the more promising results. And no doubt the reader may feel disappointed at the paucity of successful transplantations, especially if he has at all closely followed the publications of certain writers on the subject. But facts are incontrovertible, and as in the case of transplantations the facts as to results are as stated, certain views as to the advanced state of knowledge of transplantations and the established practicability of such operations are unfortunately unjustifiable (*cf.* 196). As regards practicability, the unanimous belief is held by serious investigators that hetero- or even iso- grafts, as described by vascular anastomoses, cannot be expected with present methods to give permanent results is of the greatest interest and importance in drawing conclusions as to the present state of the subject. And confirmatory of this view are the results obtained by the older and simpler method of engrafting tissues—that is, the method which consists of removing a bit of tissue and engrafting it without vascular anastomosis. For such results indicate that though a tissue may for a time retain its vitality after being removed and engrafted into a closely related animal, the time of survival is limited, and ultimately such tissues disappear. But in the writer's opinion such conclusions are perhaps too absolutely drawn. For it is well known that an autograft of this character, even though it be engrafted into an abnormal situation—at least, according to many investigators—though it may ultimately disappear—it may for a time survive and even grow. And, furthermore, he has obtained many results upon fowls that dispute such conclusions. For example, iso-engrafted ovaries in hens have been proved not only to grow and preserve normal morphologic characters, but to functionate not only in the way of supplying the evidence customarily taken as indicating the pro-

duction of an internal secretion, but fertile eggs have been obtained from such ovaries, the proof of fertility being that healthy chicks have been hatched from the eggs. These results are more fully dealt with later (p. 270).

The view has been advanced that a necessary condition for the survival of an engrafted tissue is deficiency of such tissue in the animal into which the graft is made. But the writer's results speak emphatically against this view, though it must be added that as yet proof of possible permanent multiplication of tissues or organs in an animal is lacking. And certainly the view that has been expressed that to successfully engraft the tissue for even a short period it is necessary to create a deficiency in this tissue is erroneous.

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Am. J. of Phy. = American Journal of Physiology.
Ar. of I. M. = Archives of Internal Medicine.
B. M. J. = British Medical Journal.
C. R. de la S. de B. = Comptes Rendus de la Société de Biologie.
D. Z. f. Chir. = Deutsche Zeitschrift für Chirurgie.
Jr. of Exp. Med. = Journal of Experimental Medicine.
Jr. of the Am. Med. Assoc. = Journal of the American Medical Association.
J. H. H. Bul. = Johns Hopkins Hospital Bulletin.
Jr. of Phy. = Journal of Physiology.
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CHAPTER II

SURGICAL TECHNIQUE

Introduction.

The technique here presented has been evolved from operations principally upon dogs and cats. But since no pains have been spared to avoid discomfort to the animals, it follows that the surgical measures employed are of the same character as those practised upon man in modern hospitals. The reasons for such pains are twofold—viz., humanitarian and practical. As regards the first reason, it is as evident that the unnecessary use of animals would be improper, as it is evident the employment of animals for experimentation with the view of acquiring knowledge leading to the improvement of medical and surgical practices on man is commendable. And in all cases animals are entitled to and receive the best possible treatment. Unkindness to an animal in the laboratory in any form would not be permitted. But it should be remembered that a surgical operation upon a lower animal is quite a different thing from a similar operation on man. For the psychic factor is almost a negligible quantity in properly conducted surgery upon dogs and cats. And the disagreeable after-effects due to the anæsthetic and upsetting of the balance of the nervous system by the operation itself are not only of much milder grade, but are of much shorter duration. Indeed, the slightness of the degree of discomfort manifested by animals after an ordinary major operation is rather surprising.

The more practical reasons for exercising care in animal experimentation are numerous. Not only does it avoid the wasting of materials and animals, but it hastens the answer being sought by the investigator. For example, such constancy in successful results could not have been obtained in the anastomoses of blood-vessels without such a technique. Failure would have been much more

common under less perfect conditions, which would have left the question in an uncertain state for a much longer time. For the failures would have been due to infection of the wounds, etc., and yet it would not have been clear to the investigator that such was the cause; so the experiments would have been unnecessarily multiplied and prolonged, and time needlessly wasted before perfectly definite conclusions could have been drawn.

Since it is believed that the surgeon contemplating the suture of blood-vessels in man will, if conditions permit, beforehand familiarize himself with the operation on a lower animal, a sufficiently complete account will be given to enable him to duplicate our experiments to any degree that he may desire. Therefore, if I err in the matter of details, I pray that it may be rather on the side of too many than too few.

Animal Quarters.

In experimental work on animals, receiving facilities and quarters for keeping them in good condition are necessary. In the case of dogs such quarters should consist of at least two dry, well-lighted and ventilated rooms. The location of the rooms in relation to other buildings is an important consideration. For dogs, even under ideal conditions, are apt to be noisy, and are therefore apt to be a nuisance. In large buildings the most practical location is near or on the roof, if the roof be flat, in which case it is usually possible to utilize the roof for outdoor exercise space.

The rooms should have cement or other form of waterproof walls and floors, and the floors should slope to drains to facilitate cleaning. A tap and sink should be conveniently located, and a hose and connections provided for the tap, so that the rooms may be flushed out thoroughly from time to time. A room 10 feet square will accommodate from five to ten dogs, depending upon their size. If vagrant dogs are received, they should immediately have a numbered metal tag affixed to their neck by means of a collar. For this purpose insulated copper wire is very good, taking care to wrap the ends well to avoid scratching the skin. The number should be recorded, together with the date and a description of the animal. The animal is then placed in the room with the animals most nearly of its size. It should be watched for a time to prevent its fighting or preventing any of its companions from pitching upon it. An intelligent and well-trained animal attendant will be able to quickly discover any peculiarities of an animal, and to quarter

it so as to preserve the greatest harmony in the kennels. The dog is a companionable animal, and, except in rare cases, it is better to keep a number of them together. As a rule, if there are ten dogs together, and fighting is heard, one animal is at the bottom of it, and a competent attendant will quickly locate and remove it, after which the others will soon subside. But occasionally a "killer" may be received, and such animals are sometimes hard to detect. But proper attention and tact on the part of the attendant will almost insure harmonious relations between the animals.

The quarters should be kept scrupulously clean and orderly, which requires daily sweeping and bedding. Sawdust is good for bedding, owing to its absorbent qualities. Judgment should be used in scrubbing, but it is not usually necessary to daily scrub the entire floor. While the room is being cleaned and ordered, it is well to turn the animals into the outdoor exercise space. It is best to allow the animals access to this space all the time; but if conditions do not permit this, they should be turned out as long as possible each day. Each room should be supplied with fresh water all the time. Vessels for this purpose should be of such character that they may be easily cleaned. Broad-bottomed pans serve very well. An abundance of good mixed food should be supplied daily at a regular time. Here, again, the attendant must exercise judgment in order to prevent fighting, and to see that each animal receives its share. It is well to feed outdoors if possible. The food should be placed in pans or trays, and after the animals are satisfied, all scraps, excepting a few bones, should be removed, and the vessels washed. Any bones left the next day should be removed before feeding-time. The food may be obtained from many sources, but I have found high-class hotel or restaurant scraps the most satisfactory. The animal attendant leaves one or more clean buckets fitted with lids each day at the time he goes for the feed, and the servants throw meat, bread, gravy, and potato scraps into them, so they are ready by the next day. On this diet the animals thrive better than on ordinary butcher's scraps, and it is also much cheaper.

Animals kept in confinement are especially prone to contract mange and other insect troubles, and it is necessary to exercise much care to keep them free of such pests. Mangy dogs, if received, should be isolated and washed with a mild soap and warm water, and thoroughly rubbed with sulphur ointment. A good ointment can be prepared by mixing flowers of sulphur and lard together.

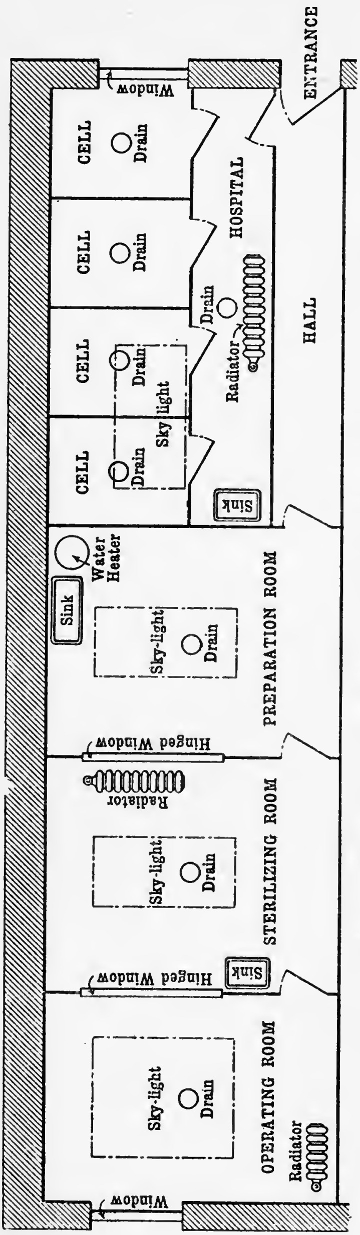

Fig. 16.—Plan of Operating-Rooms and Hospital, designed and used by Writer. Cells are provided with raised screen bottoms.

Also a careful lookout for fleas and other insects should be kept, and measures to suppress them taken. Too much caution cannot be exercised against distemper and other contagious diseases.

Under such conditions dogs will grow fat, and they may be kept in good condition indefinitely. I may say that we have kept them thus for more than five years, and they seem very contented. In fact, we have had dogs return to the kennel time and again after having been in it for a short time, after being freed.

The same general plan as outlined above is carried out on cats and other animals, with modifications to meet the peculiarities of the animals.

Operating-Rooms and Hospital.

Ideal conditions would be most nearly met by having a separate building entirely devoted to the operation of animals and their care during the post-operative period—in other words, a complete hospital for animals constructed upon the same sanitary principles as a hospital for man. With such a building, adequate grounds may be provided by the proper selection of a site. But as a rule such facilities are unobtainable, so quarters in a large building that

were adapted by the writer, and in which the majority of his work has been done, will be described. The location was in an unfinished attic space directly above a large lecture-room. A space measuring about 48 feet in length, 12 feet in breadth, and 9 feet in height, was cut off from the remainder of the attic by a solid tongued and grooved partition. Windows and a door were cut through the end brick walls, and skylights through the roof, which was flat. The space was divided by tongued and grooved partitions, and ceiled with the same kind of material. The brick walls were plastered, and cement flooring with drains put in. The details of the plan followed are given in the figure.

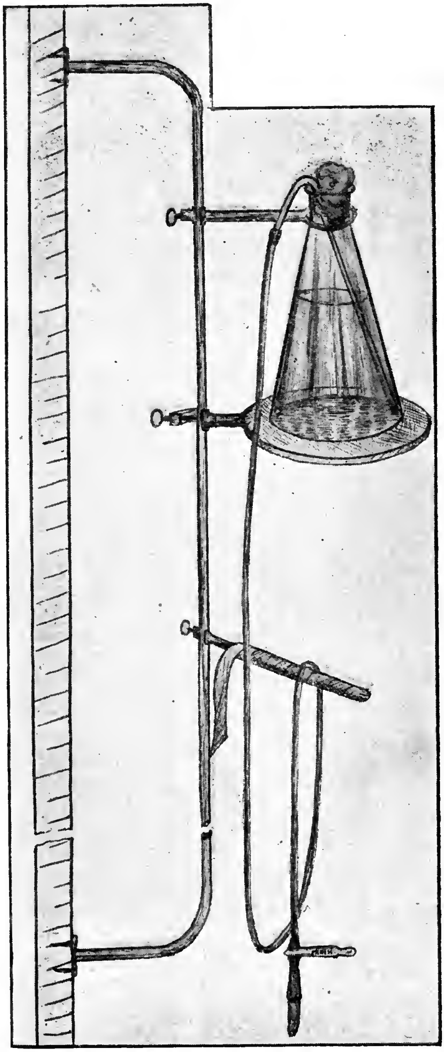

Fig. 17.—A Convenient Form of Adjustable Perfusion Apparatus.

Equipment.

The preparation-room is equipped with one or more enamelled deal tables, a basin-rack, a large sink, hot and cold water, and a large covered drain-board, upon which the animal is placed immediately after being anæsthetized for shaving, washing, and sterilizing of the operating field. Plain toilet soap, a good liquid surgical soap (such as tincture of green soap), a well-sharpened razor and a strop, absorbent cotton, gauze sponges and napkins, distilled water, antiseptic bichloride of mercury tablets, strong ethyl alcohol,

enamelled hand-basins, leg-tapes consisting of torn muslin strips 1 inch wide and 2 feet long, purified (surgical) ether, and large coarse towels, are essential. The potassium sulphite method of removing the hair has not been employed, but it is successfully employed in similar animal experimentation.

The sterilizing-room contains a sink with hot and cold water, toilet and surgical soap, brushes and a brush disinfecting pan, an instrument sterilizer of common form, a dressing sterilizer of the autoclave type or one using superheated steam, stands or tables and burners for the sterilizers, burners and tripods for boiling water, salt and other solutions, and one or more enamelled-topped or glass-covered deal tables for the preparation of instruments and dressings for the sterilizers, and a cupboard for gowns, dressings, etc.

The operating-room is equipped with an adjustable operating-table and accessories, a rack for basins, instruments, an instrument-table, a dressing-table, a heating apparatus such as a gas-stove to insure the maintenance of any desired temperature, a perfusion apparatus, compressed air or a small bellows for artificial respiration, and a movable light with reflector.

Preparation of Instruments and Materials.

The needle sused for suturing blood-vessels are of the ordinary polished steel cambric variety, ranging in size from the large No. 12, to the smallest, No. 16. The shaft of the needle tapers slightly to both extremities. The eye is small and oval in shape. Such needles are susceptible to rust, and for this reason it is not advisable to use them more than once. Needles with enlarged eye-ends are not suitable. The kind of suture material used for blood-vessel suture is very important. Fine silk is probably best for general work. There is a very great difference in silk, and only a first quality, long, smooth-fibred variety should be selected. Ravellings from silk bolting cloth, such as is used by millers for screening flour, are excellent. A similar thread is sold under the trade name of "bead silk."*

Such threads consist of three strands twisted together, and each strand is composed of two smaller strands. So the thread is made up of six small strands, and it can readily be split into three double

* Suitable needles may be procured of Kirby, Beard and Co., Ravenhurst Works, Bradford Street, Birmingham; and suitable silk of James Pearsall and Co., 71, Little Britain, London, E.C.

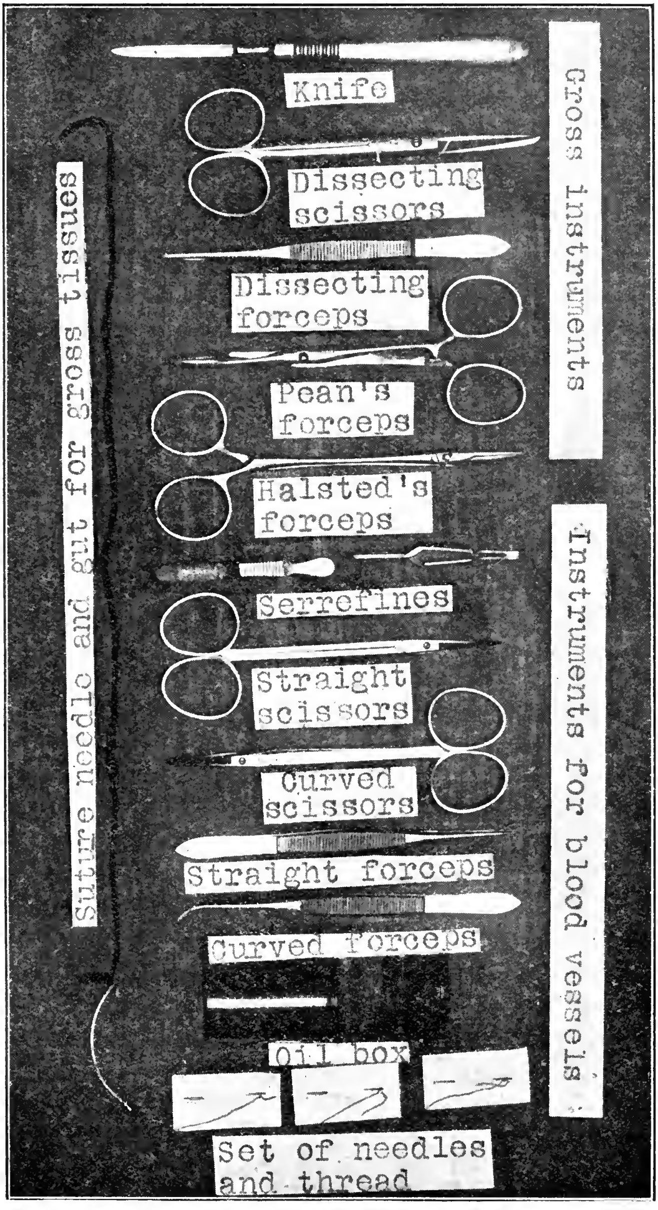

Fig. 18.—Author's Set of Instruments for Operations upon Blood-Vessels.

Only one of each type of forceps and clamps is shown.

or six single strands. The unsplit thread may be successfully employed on the larger arteries, such as the common carotid, but for smaller vessels it is better to use the single strands, either doubled or single, depending on the size of the vessel.

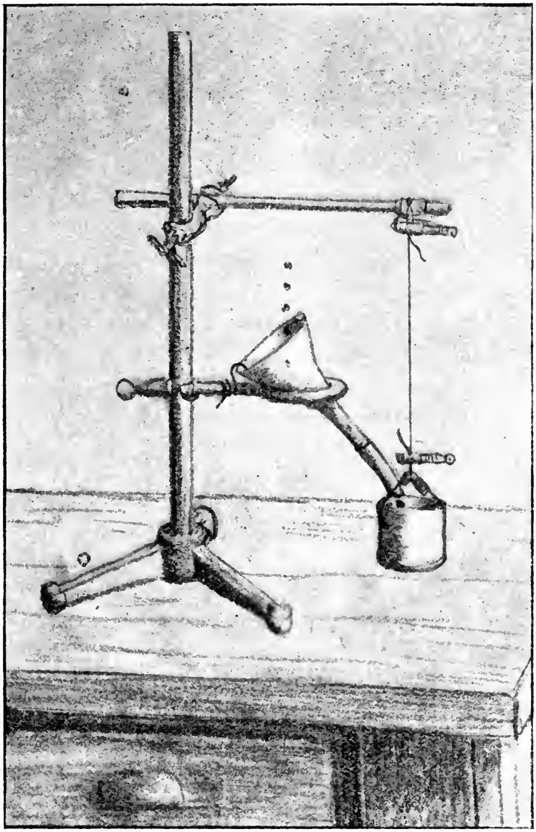

FIG. 19.—APPARATUS USED FOR TESTING SUTURE MATERIAL.

Shot are passed into the cup by means of a funnel until the thread breaks, which always takes place at a point between the clamps. The cup and contents are then weighed. The blades of the clamps and other points that come in contact with the thread are shielded with rubber.

Test for size may be roughly made by tossing the strand into the still air of a room, and noting the time required to fall through a given distance. Smoothness may be tested by taking a small stitch in the outer layer of the skin of the palm of the hand and drawing the thread through. A rough thread should not be used.

Tests for strength may be carried out by the simple method shown in the figure. The following table shows the results of some tests of this character:

SUMMARY OF TESTS OF SUTURE MATERIALS.

	Strand.	Normal.	Sterilized in Oil.	Formalin (10 per cent.).	Remarks.
		ozs.	ozs	ozs.	
SILK	1	2·83	3·08	1·91	Average of individual strands or hairs based on three or more tests. Greatest variation in test on individual strand, from maximum to minimum, about 16 per cent.
,, ...	2	3·00	3·50	3·50	
,, ...	3	—	2·83	—	
,, ...	4	—	1·91	—	
,, ...	5	—	3·58	—	
,, ...	6	—	2·41	—	
,, ...	7	3·82	—	—	
,, ...	8	3·82	—	—	
,, ...	9	2·75	—	—	
,, ...	10	2·16	—	—	
Average ..		3·03	2·88	2·70	
HAIR :					Length, 55 centimetres. Variation in breaking-point of individual hairs less than in silk. Four tests to each.
Blonde L. G.	1	4·56	4·50	3·18	
,, ,,	2	4·00	4·18	3·50	
,, ,,	3	4·37	3·50	4·37	
Average ..		4·30	4·05	3·68	
Brown E. ..	1	3·93	4·62	4·00	Length, 65 centimetres. Eight tests on normal, four on others.
,, ..	2	—	3·37	3·06	
,, ..	3	—	3·56	3·68	
Average ..		3·93	3·85	3·58	
Auburn L. 1.	1	4·56	4·31	4·12	Length, 55 centimetres. Four tests on each hair.
,, ,,	2	5·18	6·18	3·12	
,, ,,	3	5·12	4·12	4·00	
Average ..		4·95	4·87	3·75	
Auburn-Brown L. 2.	1	5·81	4·87	3·75	Length, 80 centimetres. Four tests on each hair.
,, ,,	2	6·06	4·12	4·18	
,, ,,	3	6·12	4·62	3·62	
Average ..		5·99	4·53	3·85	
Total average } Silk ..		3·03	2·88	2·70	The method of testing is shown in the figure, p. 26
Total average } Hair ..		4 79	4·30	3·71	

Taking the strain to which a strand of silk sterilized in oil may be subjected to without danger of breaking at 2 ounces, and the number of stitches placed in uniting the ends of a carotid artery of a medium-sized dog at 20 stitches, since there are really two strands

to support the load on each stitch, the total safe load that the stitches could carry would be 80 ounces. The actual load thrown upon the stitches, obtained by multiplying the cross-sectional area of the vascular lumen by the maximum pressure of the blood, would not exceed 2 ounces. Indeed, such vessels have been tested by overloading them longitudinally, and they have been observed to give way to one side of the line of anastomosis. Using the entire thread of bead silk, as has been done—*e.g.*, by Watts—since the thread is composed of six strands, the combined strength of the sutures would be about six times that of the sutures consisting of single strands. In the case of human hair the breaking-point is considerably higher than for single strands of silk.

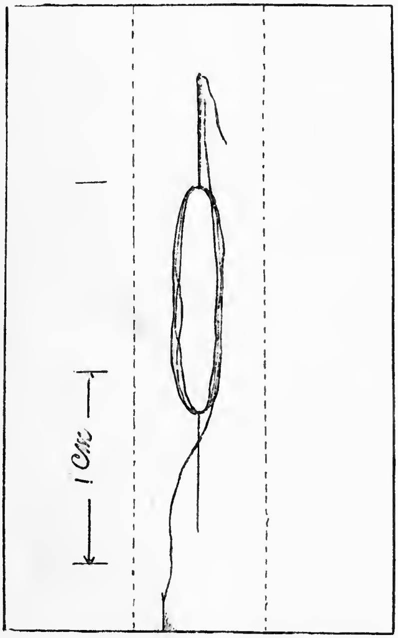

FIG. 20.—THREADED NEEDLE MOUNTED ON SLIP OF PAPER.
Dotted lines show where paper may be folded.
(*Journal of the American Medical Association*, 1910, liv. 349.)

Single threads should be tied securely into the eye of the needle, and one end clipped off to within $\frac{1}{2}$ inch of the eye. The threaded needles are wrapped on small slips of paper to facilitate handling in sterilizing. Medium weight linen writing-paper is excellent for such slips, and a large supply can be quickly cut. It may be put in a small wide-mouth bottle or vial provided with a cork, and kept on hand if needles and thread are to be prepared for each operation. But a more convenient plan is to prepare a supply for some months at least, and after sterilization to put them away, so that they may always be ready. This may conveniently be done by folding the papers about the needle, as shown in the figure, to protect the thread and points of the needles, and inserting three together into small glass tubes containing heavy paraffin oil, and sealing the tubes and sterilizing by boiling. The oil may be previously rendered slightly antiseptic, but, if so, all excess should be

wiped from the needles and threads before using them on blood-vessels. If no antiseptic is used, the surplus of oil in the tube will come in handy for using on the blood-vessels to prevent drying during the time of the operation and to facilitate successful suturing.

If the needles and threads are prepared along with the other instruments for each operation, a plan that I have largely followed, an ordinary brass screw top microscope objective-box makes an excellent receptacle for holding the oil in which they are sterilized. Also by this method an abundance of sterile oil is assured without special thought or preparation. And the top of the box, set down like a cup, makes an excellent container for the oil used at the operation. Owing to its shape, it is not liable to be overturned, since it has a broad, flat base when thus used. Being small and compact, it may be placed close to the field of operation; and as it is shallow, the finger can be readily dipped into the oil. A disc of good quality of cork, which may be cut from one end of a stopper, should be snugly fitted inside of the top, the smooth surface of the disc being faced downward, so that, when the top is screwed on the box, a tight joint will be formed between the margin of the cork disc and the edge of the side of the box. This is important to prevent the entrance of water into the box during sterilization. With the box about three-fourths full of oil, the papers bearing the threaded needles are dropped in, and the lid screwed on firmly. The box is then set in the solution of sodium carbonate in one corner of the instrument sterilizer, and boiled with the instruments. After sterilization is complete, the box should be removed (under aseptic technique) and the lid unscrewed, and both the box and lid set on the sterilized covering of the instrument-table. For if the

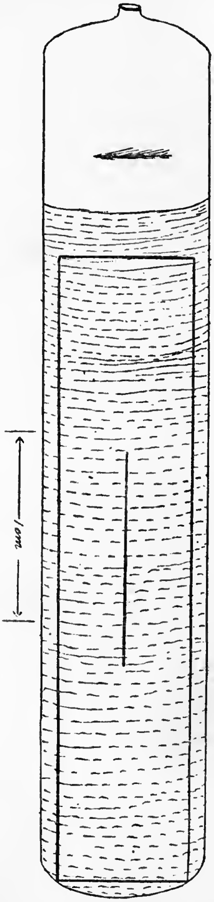

FIG. 21.—PAPER PACKAGE CONTAINING NEEDLE AND THREAD, PREPARED AS IN FIG. 20, IN SEALED GLASS TUBE CONTAINING STERILE OR ANTISEPTIC PARAFFIN OIL.
(*Journal of the American Medical Association*, 1910, liv. 349.)
Scale in centimetres.

top should fit imperfectly, if left in the sterilizer after it began to cool, liquid might be drawn into it owing to the formation of a partial vacuum. Before being called for in the operation, the papers should be removed from the oil in the box, and the excess of adherent oil drained back into the box. Ordinary sterilized dissecting forceps are suitable for removing the needles from the box. The threads are then unwrapped by sterilized hands, and the needles and threads laid parallel on a smooth lint-free surface. The needles should not be withdrawn from the papers on which they are mounted, as the papers facilitate handling in passing to the operator. The nature of the surface upon which they are laid is important, especially as regards the absence of lint. Also a dark surface is better than a light one, as the threads are more readily seen, and therefore tangling and snarling is easier to prevent. A sheet of black oiled cloth, or a sheet of glass laid on a dark cloth, answer very well. Black suture material would, perhaps, be somewhat easier to manipulate than white, as in the bright light of the operating-room it would show more plainly. These latter considerations, though possibly appearing as trifling to the reader, are of distinct importance when the finest ligatures are employed.

Human hair in several ways fulfils the requirements of an ideal vascular suture material, as in homogeneity, fineness, strength, and smoothness. Perhaps the simplest method of preparation would be to sterilize the needles and hair in formaldehyde solution, and to apply sterilized oil just before using. We have employed this method, using 10 per cent. formalin, with perfect results. But hair may be sterilized in hot oil the same as silk. To be in the best possible condition for handling, the hair should not be kinked; therefore it should not be wrapped or curled tightly in its preparation.

Bull-dog forceps or serrefines are generally satisfactory for temporary occlusion of blood-vessels, and a sufficient number should be prepared for the operation to be performed, the number depending upon the nature of the operation. For example, in a simple end-to-end anastomosis but two are required. But several extra ones should be prepared, so that in case one is accidentally dropped upon an unclean surface, or for other unforeseen reason, the exact number deemed necessary should prove to be too small. The most useful size measures about 60 millimetres in total length. The blades are about 20 millimetres long and 5 millimetres broad. They taper slightly to the point, which is rounded. The outer surfaces are rounded and smooth, and the inner surfaces flat and transversely

corrugated. The corrugations number about two to the millimetre, and are shallow. The spring should be of such strength that, when the skin of the flexor surface of the forearm is grasped by the points, the points being separated by about 10 millimetres in applying to the skin, no sharp pain is produced in ten seconds. The blanching of the skin and the marks of the corrugations will disappear within thirty to sixty seconds after the removal of the forceps if the spring is of the proper strength. If the spring is set for too strong a pressure, this may be corrected by forcing them

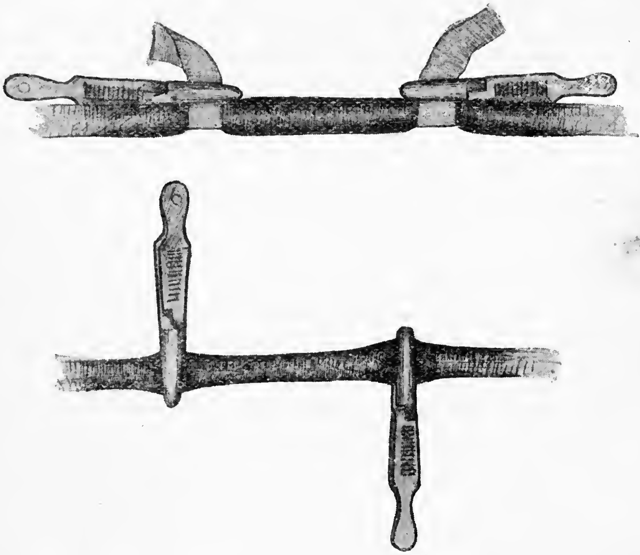

Fig. 22.—Showing Two Efficient Methods of Temporarily Occluding Vessels for Suturing.

together with a pair of pliers ; or, if too weak, they may, of course, be made stronger by forcibly separating them.

On medium-sized blood-vessels, for example, the common carotid artery or external jugular vein of a 15-kilo dog—such forceps may be safely applied directly. But the vessel should be grasped near the point of the blades, as the pressure exerted by the spring is, of course, greater near the base of the blades. It is better, however, to either face the blades with muslin, fastening it to the blades by sewing or wrapping with a thread, or by passing a narrow thin tape or strip of cloth about the vessel at the point to be occluded, and while exerting gentle traction upon the two ends, in order to

bring the cloth into snug contact with the vessel, to apply the forceps over the material.

Another method of temporary occlusion which presents the advantage of requiring no special kind of forceps is carried out by means of a narrow strip of tape or cloth, which may be cut or torn from almost any sterilized cloth used at a surgical operation. The cloth tape or strip is passed around the vessel as in the preceding description, and the ends grasped in one hand. With the other hand the slightly opened blades of a pair of light hæmostatic forceps are placed on either side of the doubled tape, and by a stripping movement the vessel is occluded between the walls of the tape. The tape is then clamped snugly against the vessel until the forceps lock. With a little practice this, perhaps, is the safest method of temporary occlusion yet devised, as no metallic pressure is even indirectly exerted upon the vessel. And less pressure is required by this form of compression to prevent retraction of the vessel after it is divided. In this respect cloth-faced forceps are superior to unfaced ones, as cloth adheres more tightly to the tissues of blood-vessels. Owing to the well-marked tendency of blood-vessels, especially arteries, to retract after division and slip from the blades of forceps or other compression instruments applied for temporary occlusion only, the holding power of cloth in this respect enables the operator to very materially reduce the difficulty introduced in the successful anastomoses of blood-vessels by their retraction tendencies. And for this reason rubber-faced instruments should not be used, as rubber becomes very slippery when moistened with blood or tissue liquids.

For temporary compression of a blood-vessel that is not to be divided, and hence in which retraction is not a factor, a most excellent method consists in passing a coarse linen or silk ligature around it, and bringing the ends out of the wound. Then, by mere traction upon the ends of the ligature, the circulation through the vessel may be controlled at will. But a preferable though more complicated method is to draw the two ends of the ligature through a piece of tubing having smooth ends, as a piece of glass tubing, the ends of which have been smoothed and rounded by fusing. The tube is of such length as to reach from the surface of the skin, where the superficial wound is made, to the vessel. It is pushed into the wound until the end rests against the vessel. Traction on the ligature, the ends of which should be tied together to insure its not being accidentally withdrawn from about the vessel,

will then neatly and safely constrict the vessel against the end of the tube. Tension on the ligature may be maintained by grasping both strands of the ligature with serrefines or other light forceps, the blades of which are placed crosswise the end of the tube and in contact with it. After placing the tube in position, the wound may be closed about it, as it can be withdrawn, and the ligature cut and withdrawn in an instant. If necessary, a single stitch in the skin will then finish closure of the wound, or a metallic skin-clip may be used. But if a tube of proper size is employed, no such suture will be necessary, as the tissues will, in virtue of their elasticity, fill the space previously occupied by the tube.

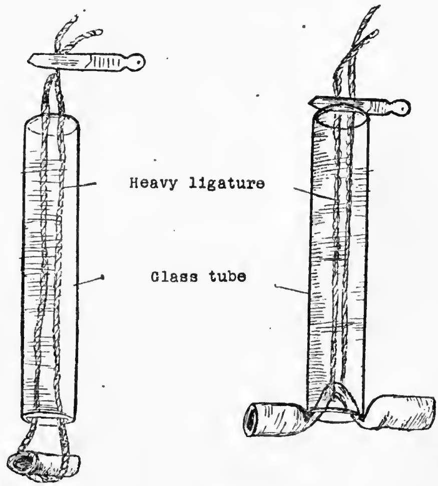

FIG. 23.—SHOWING METHOD OF TEMPORARY ARTERIAL COMPRESSION BY MEANS OF A SNARE.

For aid in handling the tissues of the blood-vessels and the needles and thread in suturing, two light, slender, curved, or one curved and one straight, dissecting forceps are invaluable. The points should be fine, but not sharp. They are the type of forceps used in making the finer dissections in studying the anatomy of frogs and such animals, and they may therefore be obtained from any first-class biological laboratory supply-house.* A pair of small scissors, also used for such dissections, are very useful for working on blood-vessels. The blades are sharp-pointed and keen, making a clean cut, with little crushing. Two pairs of medium straight surgical dissecting forceps, a medium pair of ordinary surgical scissors for general dissection, and a pair of fairly large scissors for rougher work, such as cutting cloth, are prepared. Two surgical knives of the narrow, hollow-ground, straight-bladed (spear-point) English form; six pairs of medium hæmostats; six pairs light hæmostats (Halsted mosquito); and one straight and one curved, slender-jawed, heavy hæmostats, are also prepared. Two large,

* The form sold by Bausch and Lomb, of Rochester, New York, is excellent.

two medium, and two small curved triangular-pointed suture needles complete the list of surgical instruments generally employed for operations for suture of blood-vessels. The instruments are sterilized by boiling in dilute sodium carbonate solution for at least ten minutes. They are removed immediately from the sterilizer, and assorted and arranged on the instrument-table. Any excess of solution remaining on them after cooling for a short time is removed with a sterilized cloth. The use of much sodium carbonate in the water, to prevent rusting, is to be avoided, as it is unnecessary. And if much of the salt is used, the instruments will be so heavily coated with it after they have dried that they will have to be gone all over with a cloth in order to be in good condition for the operation, which is bad both from the standpoints of time and of asepsis.

Ligature and ordinary suture material may be prepared, or the commercial, aseptically prepared, may be used. Quite a number of commercially prepared catguts have been used, and they have all been satisfactory. One of the most satisfactory, owing to its pliancy, is that prepared under a method published by Dr. Willard Bartlett. A slowly absorbable gut should be used, especially in the outer tissues. For example, if an extensive abdominal opening in a cat is closed with a quickly absorbable gut, the chances are very great that the wound will open. As to size, No. 2 is the most generally useful, but a size smaller may be used on cats or other small animals with good results. A half-dozen 8-inch medium twisted or braided silk ligatures and a dozen fine twisted silk ligatures are prepared along with the instruments. They may be simply boiled in the carbonate solution with the instruments, but as a rule I put them in the box with the needles and thread, as they handle nicely when taken from the oil, and the results are good. In case they are boiled in the carbonate solution, they are rinsed with sterilized 0·9 per cent. sodium chloride solution before being used. Whether this leads to better results I do not know, but since the sodium carbonate impregnation is an untested factor with us, I prefer to rinse with the sodium chloride, even though there is no reason for anticipating any observable difference in the results.

The suture and ligature materials are arranged on the table along with the instruments, if all are prepared at the same time. In the case of commercially prepared gut, the technique ordinarily employed by surgeons is followed, which varies somewhat with different forms of gut. But sufficiently explicit directions are

usually found upon the wrapper in which it comes to enable the operator to use it properly.

Gowns, table-covers, operating-cloths, towels, napkins, absorbent and plain cotton, gauze, cotton-gauze sponges, oiled silk, roller bandages, and the like, are so nearly of the ordinary surgical type that very little description is necessary.

A list of cloths and materials prepared for the operation is as follows: Four gowns; one heavy muslin cover, 24 by 24 inches, for instrument-table; four heavy muslin covers, 26 by 36 inches, for operating table; one heavy muslin cover, 32 by 50 inches, for dressing-table; four, 20 by 30 inches, heavy muslin cloths for covering animal; one dozen, 16 by 32 inches, soft hand-towels; half a dozen heavy hand-towels; one dozen, 14 by 14 inches, soft napkins; one roll absorbent cotton; one roll plain cotton; two dozen cotton-gauze sponges, size hen's-egg; 1 yard gauze; three pieces oiled silk, 6 by 4 inches; one 5 yard 2-inch rolled bandage; 1 yard heavy unbleached muslin for making tailed bandage for completing dressing. A bottle of powdered boric acid is placed conveniently for dusting the wound before dressings are applied.

The gowns, operating-cloths, and dressings are sterilized in live steam for twenty minutes or more at a temperature of at least 120° C., after which they are removed, and spread out on the table placed in the operating-room for that purpose.

Preparation of Animal.

Animals in good condition should be selected for best results. If very dirty, they should be washed the day preceding operation in a warm room in warm water, using a mild toilet soap. The bath should occupy a short period, and the animal should be quickly and thoroughly dried with towels, and then placed in a clean compartment in the hospital. The purpose of the bath is for the removal only of the excess of dirt, and it is not to sterilize or render the coat aseptic. Only the hands or a sponge are to be used, as harsher measures, as scrubbing with a brush, is very liable to lead to an irritated condition of the skin. After the bath the animal is supplied with clean bedding, excelsior, covered with a clean coarse bag, or other coarse cloth being excellent. A moderate amount of food and plenty of water is placed before the animal. Water, but no solid food, is given on the day of the operation.

The hours from 10 a.m. to 3 p.m. are the best for operating on account of light, but this depends to a large extent upon the

direction of exposure of the windows. When all is ready, the animal is brought into the preparation-room either by leading or carrying in a large coarse bag. In general, the most satisfactory method of handling animals in taking them from place to place is to put them in such a bag. The mouth of the bag is tied so that when laid upon the floor the animal cannot get out.

Anæsthesia is quickly and humanely produced in the following manner: One or more heavy towels are spread upon the floor; a flake of cotton batting, as large as the two hands, is then placed on the towel about one-fourth of the length of the towel from one end. The towel is then folded in the middle, so that the two ends come together. The dog, having been removed from the bag, is then stood with its nose over the towel. The anæsthetist kneels or squats to the right of the animal, and grasps the skin of the nape of the neck gently with his left hand. An assistant takes position to the left of the animal, and grasps both fore-legs just above the feet with his left hand, and both hind-legs similarly with his right. The anæsthetist then pours ether upon the towels at the point above the centre of the flake of cotton. Enough ether is poured on to saturate the cloth and cotton thoroughly for a space as large as the hand. The ether-can is quickly set aside, but in convenient reach, and both hands of the anæsthetist placed firmly about the animal's neck, and the head laid upon the towels so that the nose lies over the centre of the ether-saturated portion. The assistant at the same time draws the legs from under the animal, so that it is laid upon the floor gently and quickly. The anæsthetist instantly removes the right hand after the animal is laid down, but the left is held firmly on the neck, pressing downward and forward so that the fingers are under the angle of the jaw, and therefore out of harm's way. With the right hand the towels are thrown over the throat, and pulled well back on the neck, and held by placing the hand against them, and thus grasping the neck with the thumb pressing behind the left ear, and the index-finger behind the occiput. The left hand is then quickly snatched backward and out from under the towel, and replaced in its former position, only this time on the outside of the towel. The thumbs of the two hands come together behind the occiput, while the fingers encircle and gather in and firmly hold the towel beneath the animal's throat. The assistant keeps the fore- and hind-limbs well separated. By this method practically all excitement of the animal is avoided, and the period of struggling is very brief. Indeed, the animal usually is com-

pletely anæsthetized in less than one minute, and the method is very safe.

As soon as the animal is anæsthetized, it is placed upon the drain-board in connection with the sink, and the field of the operation rubbed with liquid soap and shaved. A few strokes of a well-sharpened razor properly applied—that is, with a sliding stroke from the point toward the heel—will remove the hair from a large area, and leave the skin in excellent condition. Previous clipping of the hair is unnecessary. The stroke of the razor should always be in the direction of the hair. Also traction should be exerted on the skin, so that it may be stretched under the edge of the razor. This is conveniently accomplished by placing the hand on the skin back of where the razor is started.

After the hair is removed, the shaved area is washed with more of the surgical soap solution and water, using a cloth or cotton sponge, and all excess of moisture removed first from the shaved surface, which is uppermost, and then the surrounding portion of the coat. A little strong alcohol (95 per cent.), or alcohol-ether mixture, is then used on the shaved area to remove fatty substances and to aid in sterilizing, and this is followed by a pad of absorbent cotton saturated with 1 in 1,000 bichloride solution, the pad being applied to the whole of the shaved area, and pressed lightly against the skin.

Looped tapes having been affixed to each leg immediately above the ball of the foot, the animal is carried in to the operating-room and placed upon the table, which is covered with a waterproof cloth, to protect the enamelled top from the action of alcohol which is subsequently used, and to keep the animal from undue cooling from direct contact with the table-top. The tapes upon the feet are then fastened in the holes of the frame of the table-top and suitable sand bags in waterproof covers placed about the animal to keep it in position. One placed longitudinally on either side of the thorax and one transversely under the neck suffice ; but if operating upon the abdominal vessels, one such bag should be placed transversely under the back below the point of operation. A rubber hood is then placed over the head and firmly fastened around the base of the neck, but care must be taken not to make it so tight as to interfere with either circulation or respiration. The extremity of the hood is tightly fastened to the margin of a metal funnel, so that by connecting the stem of the funnel with an anæsthetic bottle by means of a piece of flexible tubing the administration of ether becomes almost automatic. Or in place of the

hood a tube may be passed through the larynx into the trachea and similarly connected with the ether bottle (see p. 306). The tube is held in place by a coarse, soft ligature, tied first about the shank of the tube and then around the lower jaw of the animal behind the canine teeth. The tube is easily inserted into the larynx. In a good light, the neck is moderately extended and the tongue grasped with a cloth and pulled forward. This raises the larynx and brings the glottis plainly into view if the jaws be separated and the head held towards a window, so that light may shine down the animal's throat. It is well to insert

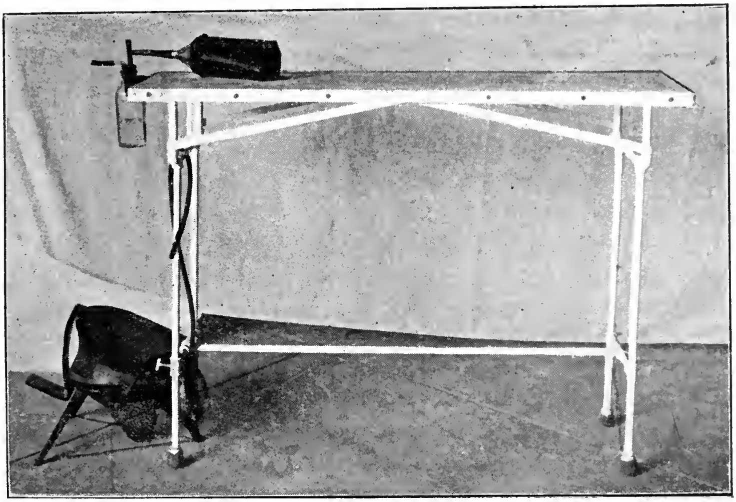

Fig. 24.—Operating-Table, with Arrangement for giving Anæsthetic. Also Bellows for giving Artificial Respiration, if required, is shown.

a piece of soft wood in the corner of the mouth on one side between the jaw teeth to prevent accident while inserting the tube. The laryngeo-tracheal tube is in several respects superior to the hood method of giving an anæsthetic, especially on small animals; for not only is the surgical field less encumbered—especially in operations upon the neck or about the head—but the lungs are in unobstructed communication with the outside during the entire course of the operation, and no obstruction can be produced, as by the accumulation of mucus in the pharynx or the walls of the larynx coming together, which sometimes are serious complications in general anæsthesia; nor can gastric liquid or other material enter the lungs

in case of vomiting, as may happen under other methods. Finally, in case of respiratory failure, efficient artificial respiration may

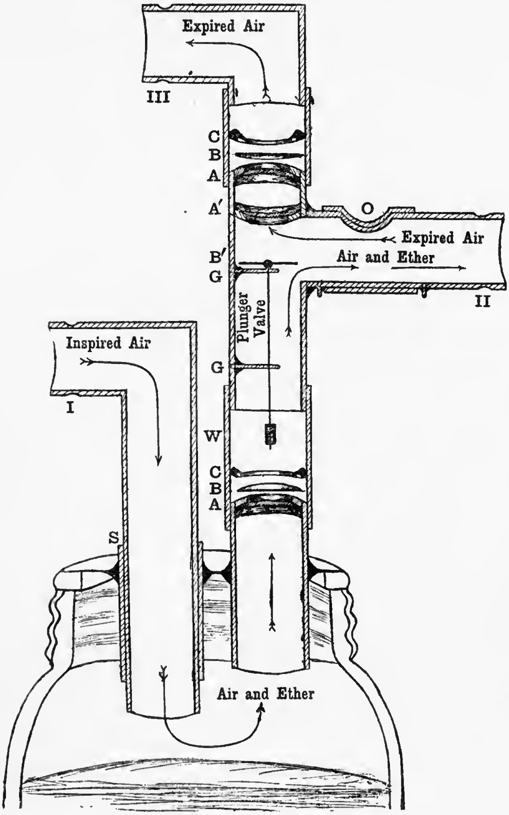

FIG. 25.—RESPIRATION VALVES.

I. Entrance for air into anæsthetic bottle. S, Collar in which tube slides for adjusting the amount of ether.
II. Connection for laryngeal or tracheal tube. O, Opening in tube and movable collar for adjusting the admixture of air.
III. Outlet for expired air. By connection with gasometer the amount of expired air can be measured; or by connection with spirometer, the expired air can be measured and collected for analysis. A marker may be connected with the spirometer, and arranged to show on a moving surface the amount of expired air.
A, Valve seat; B, valve disk; C, valve stop; B′, valve to close the opening at A′ when artificial respiration is given by means of rhythmic or positive pressure through I; W, weight for regulating the action of valve in forced artificial respiration.

immediately be given, and at such times seconds are precious. But in using this method too large a tube should not be employed, and reasonable care should be exercised to avoid straining or injuring

the larynx in any manner. I have used the method many times, and have yet to observe a single bad after-effect attributable to it.*

A pair of bellows or a compressed air-supply are available for use in operations necessitating the opening of the pleural cavities or for giving artificial respiration as occasion may demand.

The operation itself is carried out with the aid of an anæsthetist, an assistant operator, and an instrument and dressing passer. All are clothed in sterilized gowns, and the heads of the operators are covered by caps made from towels by tying two opposite corners together behind the head and folding down the other corners and pinning into place. Gloves are not worn, but the hands and forearms of all but the anæsthetist are thoroughly washed, sterilized in bichloride of mercury solution and alcohol, and then rinsed in sterilized water.

The anæsthetist is provided with a stool and placed at the head of the table. In addition to regulating the anæsthesia he handles the animal, as may be necessary during the operation, by placing his hands beneath the sterilized coverings. Also he keeps written notes of the operation. The operator stands to the right of the table, and faces the anæsthetist. The table is so placed that the side-light comes from the operator's side of the room. The assistant stands on the other side of the table, so he is between the operating- and dressing- and instrument-tables. The instrument and dressing passer is stationed close to the assistant and within easy reach of the instrument- and dressing-tables. The bichloride dressing is then removed from the shaved operation field and the area sponged with alcohol, and a thin pad of absorbent cotton saturated with alcohol applied to the shaved surface. Supposing that the operation is to be ligation and division of both common carotid arteries and anastomosis of the central end of the right to the peripheral end of the left, the shaved area will extend from the cricoid cartilage above to about an inch below the anterior end of the sternum, and well down on either side of the neck. The sand-bag, previously placed transversely beneath the neck, should cause extension of the neck backward below the point selected for division, and any such adjustments necessary are made by the anæsthetist, who carefully avoids touching the shaved area. The trunk of the animal is now covered by at least two thicknesses of heavy sterilized cloth, which

* For illustrated account of method of giving anæsthetic to animals, see *Jr. A. M. A.*, 1911, lvii. 887.

extends over the edge of the table. The head down to the upper margin of the shaved area is covered by similar cloths or towels, placed transversely so as to cover the entire anterior end of the table. Then a heavy towel is placed longitudinally on either side of the neck, so that the inner edges come together in the mid-line both above and below the shaved area. The edges of these towels are then grasped together with the underlying cloths, and fixed with forceps (Pean's are good, owing to the spring of the blades) about an inch both above and below the margins of the shaved area. The cotton pad is then removed from the shaved area, and after rinsing the hands again in the antiseptic solutions and water, the operation itself is begun. The animal is, of course, completely anæsthetized, which condition is maintained until after the wound is closed.

With a knife held between the tip of the thumb and fingers, so that the cutting edge is almost parallel with the surface of the skin through which the incision is to be carried, and with the skin fixed to prevent it sliding and following the knife, which is accomplished by pressing with the thumb and forefinger of the left hand at a point on a level of and to either side of the anterior point of the proposed incision, the skin is divided in the mid-line by a single, firm, continuous stroke of the knife, from about an inch below the cricoid cartilage to near the upper end of the sternum. If properly made, the skin and adherent subcutaneous tissues will be completely divided, and a very slight amount of hæmorrhage will occur. But however trifling the hæmorrhage, it is lightly stroked with a dry cotton-gauze sponge and, if need be, lightly compressed until the wound is dry. While this is being done the anterior and posterior extremities of the incision are grasped by Pean or other strong forceps together with the inner edges of the longitudinal and laterally placed towels, and skin and towels fixed together. The handles of the forceps in both cases extend away from the points of the incision. Next, two or more similar forceps are made to grasp and fix the skin and edges of the towels together at opposite points along either side of the wound, with the handles placed outward, so that nothing is exposed but the structures appearing in the bottom of the wound. With a few light strokes of the knife the inner margins of the sterno-hyoid muscles are exposed, and the anterior median vein, lying between them, comes into view. With a pair of blunt dissecting forceps in either hand, and using them as blunt needles with the blades closed, the inner margins of the sterno-hyoid muscles are

separated, the median vein being left attached to the one to which it seems most tightly adherent. Venous branches of any considerable size, running to the opposite muscle, are then crushed or stretched until they are divided, and any hæmorrhage controlled by applying hæmostats to the bleeding-point. Bleeding from these vessels is usually slight, and when the hæmostats are removed, as a rule no further escape of blood occurs from the divided vessels. The tissues down to the anterior surface of the trachea are then separated by means of the blunt dissecting forceps, used as before, until a space large enough to admit the tips of the index-fingers is made. The fingers are inserted back to back and slightly flexed so that the tips hold in the tissues. Then, by careful but firm traction, with the fingers acting in opposite directions, the tissues are pulled apart until the trachea is exposed for nearly the whole length of the wound. Working first on one side and then on the other, in a similar manner the carotid sheaths are exposed. Notwithstanding the extensive separation of tissues thus quickly accomplished, not a drop of blood need be shed. The forceps holding the skin and towels together at the sides of the wound may now be released and reapplied to also include the tissue bordering the inner margins of the sterno-hyoid muscles, thus exposing more effectively the deeper structures; or, without disturbing the forceps holding the skin and towels, additional forceps may be used to fix the margins of the muscles to the towels, which is perhaps a somewhat better procedure if sufficient forceps are on hand. Each carotid artery is in turn picked up by passing the point of the left index-finger beneath it, and, if the operator be sufficiently expert, the artery is exposed and freed from the internal jugular vein and vagus nerve by delicate use of the knife. Or closed blunt dissecting forceps may be used to separate the artery. It is strongly adherent to the nerve, and care must be taken to avoid straining or injuring either of the structures.

After the arteries are freed for the entire extent rendered accessible by the wound, they are grasped and crushed with heavy, tapering-jawed, hæmostatic forceps, the right high up so as to give a long central end after division, and the left low down so that it may have a long, free peripheral end. Strong, but not very coarse, silk ligatures are then passed about each artery in turn, and the vessels firmly and securely ligated, in the case of the right artery above, and in the case of the left artery below, the hæmostatic forceps. The ends of the ligatures are then cut off within $\frac{1}{8}$ inch of the vessels.

A pair of bull-dog forceps, previously tested as to strength, and preferably having cloth-covered blades, are applied to each artery, in both cases at as great a distance as possible from the corresponding hæmostatic forceps previously applied.

The vessels are then transversely divided with a single, firm rapid movement of the blades of a pair of small, keen scissors, the line of division in each case being within a few millimetres of the hæmostatic forceps. After dividing one vessel, it is stripped several times between the balls of the finger and thumb, from the serrefine

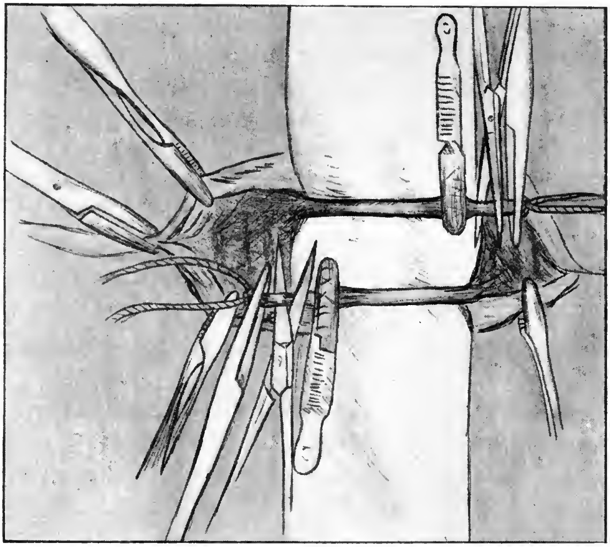

FIG. 26.—END-TO-END ANASTOMOSIS.

Carotid arteries exposed, permanent ligatures and temporary hæmostatic forceps applied, with scissors in position, to show preparation of vessels for anastomosis of the central end of the right to the peripheral end of the left. Drawing from photograph. Through an inadvertence the temporary clamps appear too near to the scissors. See following figures.

to the cut end, over which a dry cotton-gauze sponge is held. After all excess of blood is thus removed, a little oil is applied to the end of the vessel with the finger. The second vessel is then divided and treated in exactly the same manner. The hæmostatic forceps on the ligated ends of the vessels are now removed, and the wound wiped out gently with a dry sponge.

A strip of waterproof material, having a lint-free surface, and sufficiently wide to cover the floor of the wound, is placed transversely in the wound, and the ends of the vessels to be anastomosed

are brought close together on its upper surface. Oiled silk or other similar cloth, or rubber-coated cloth, serves well for this purpose. If the material be black the threads used for anastomosis may be more easily seen, and it will be less fatiguing to the sight.

Anastomosis of the Vessels.

The operation of anastomosing is now begun. The end of each vessel is examined in turn, and the loose outer sheath is slipped back for a few millimetres from the end. It may be that the end of the vessel is covered by this sheath, in which case the excess is removed by grasping the loose tissues over the end of the vessel with the ball of the left thumb and forefinger, and, while exerting light traction, to snip off the excess with sharp scissors. The outline of the end of the vessel will show plainly, and the cut is to be made distal to it. When this is done, the outer loose tissue remaining is pushed back from the end of the vessel as before described. The fingers alone are used for such handling of the vessels. After the ends of both vessels are thus prepared and inspected to see that they are cleanly and evenly cut, and that they are free of blood, either liquid or clotted, and any such undesirable conditions remedied by the methods already described, the operator lightly oils his fingers, which should be clean and dry, and then begins placing the three fixing sutures. The vessels are examined to see that they are not twisted, and then picking up the central end of the right artery, a needle carrying a vascular suture is thrust through the middle of the posterior wall, within $\frac{1}{2}$ millimetre or less of the free cut surface from without inward, taking care to penetrate all the coats, including the intima. After penetrating the intima, the point of the needle

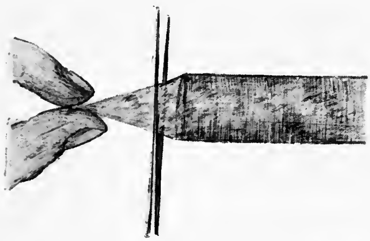

Fig. 27.—Showing Method of Removing Excess of Perivascular Tissue from an Artery after Division, preparatory to Anastomosis.

(Diagrammatic.)

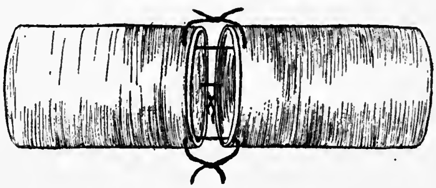

Fig. 28.—Showing Position of Primary Fixing Sutures in End-to-End Anastomosis of Blood-Vessels.

is directed anteriorly so as to avoid the opposite side of the vessel wall. If, by light traction, the assistant can bring the ends of the two vessels close together, the point of the needle is then directed dorsally, and made to penetrate the corresponding points in the mid-line on the posterior wall of the peripheral end of the left artery, from the intimal surface outward. The point of the needle is then grasped between the left thumb and forefinger, and the ligature drawn about halfway through. A single knot is then tied in the ligature, so that but little traction may be exerted on the

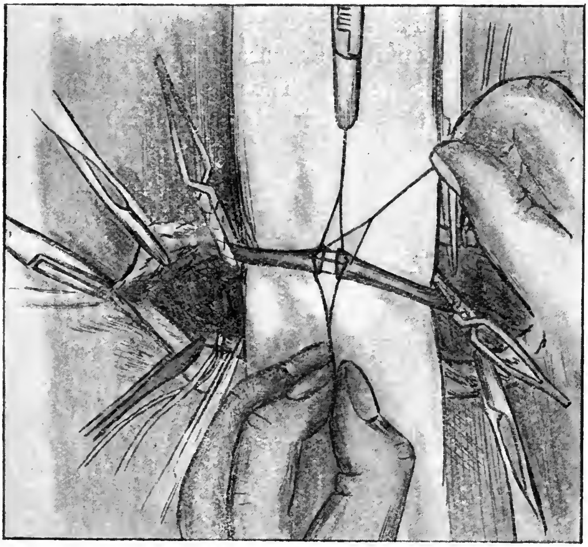

Fig. 29.—Apposition of Ends of Divided Arteries by Means of Stay Sutures, preliminary to Continuous Stitching together.

(Drawing from a photograph.)

ends of the vessels, and the free ends are held by the assistant, who draws them toward the left side of the animal, which produces a quarter twist in both ends of the vessels. The operator now places the second fixing ligature, which, being one-third of the circumference away from the first one, will come almost on the uppermost point on the circumference of the vessels as they are being held by the assistant. The direction of the needle is the same as in the first instance, but the ligature is more easily placed as the vessels are in a more favourable position. A pair of light, tapering forceps may now be used by the left hand to press the tissues back as the needle

is thrust through. This is done not by grasping the tissues, which is to be avoided, but by pressing against the tissues with the side of the closed blades. As soon as the point of the needle is through the walls of both vessels far enough to be grasped, it is seized with the forceps and drawn through, and the ligature tied loosely, as in the case of the first one ; but if the cut edges of the vessels may be brought together with little or no resistance, the two ligatures may be firmly tied before placing the third one. The assistant now drops the end of the posterior ligature, and the operator pulls the ends under the vessel to the right side of the neck by reaching beneath the vessel with a pair of light, curved forceps, and passing the curved surface about the ligatures and drawing them underneath and out from the vessel. The assistant now holds the first ligature, which is also the posterior, but which is now drawn to the right side of the neck, in the fingers of the right hand, and the second ligature, which is the left side of the vessel when the vessel is in its natural position, in his left hand, and exerts very gentle but firm, steady traction upon the vessel, which should not be more than is necessary for slightly lifting the point at which the anastomosis is being made from the waterproof covering over the floor of the wound. The operator then places the third and last fixing suture through the margins of both ends of the vessel, at a point equidistant from the first and second sutures, using the same technique as in the placing of the second. The ligature is then tied, which ends this stage of the operation.

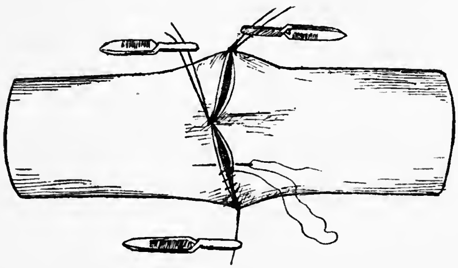

Fig. 30.—Showing Tension Sutures and Continuous Stitches partially placed in the Union of the Ends of Blood-Vessels.

The operator next grasps both strands of the posterior ligature and separates the two ends. The needle is used for sewing the edges of the vessels together and he takes it in the fingers of his right hand, while the other end of the ligature is held by the fingers of his left hand, and by means of it he exerts gentle traction against the ligature placed in the right side of the vessel—the last one to be placed—both ends of which are grasped by the fingers of the left hand of the assistant. With his right hand the assistant manipu-

lates a pair of light, tapering, curved or straight dissecting forceps, and not only presses against the tissues of the blood-vessel as the operator thrusts the needle through the walls, but as soon as the needle is through to the extent of about one-third of its length he grasps the bar of the needle with the forceps near the point of exit from the tissue and pulls it through. The operator places the stitches through the margins of the walls of the cut ends of the vessel, as in the placing of the fixing sutures. The stitches are placed so that inside the vessel the thread will be at right angles to the line of anastomosis. Care is taken to actually see in every case

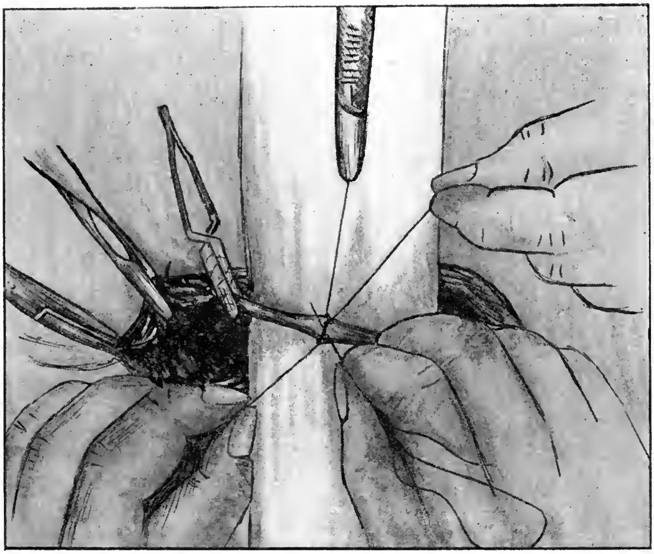

Fig. 31.—Stitching Between Stay Sutures shown in Fig. 29. The needle is turned obliquely for purpose of better illustrating. (Drawing from a photograph.)

that the stitches include all the coats of the walls of both vessels and that no loose outer tissue gets between the cut surfaces of the vessels. As soon as the needle is drawn through by the forceps of the assistant, it is immediately seized again and the stitch drawn until all slack is removed. The next stitch is then placed in the same manner, and the process repeated until the doubled ligature held by the assistant is reached. The suture is then tied with a double knot with the doubled fixing ligature. A pair of serrefine forceps are then attached to the end of the posterior ligature that has been held by the fingers of the left hand of the operator, after

which the end of the ligature is released. The main purpose of the serrefine, is to act as a weight so that when traction is made upon the other two fixing ligatures by the operator and assistant, the vessel, being not only stretched between the ligatures transversely, but lifted up so that the serrefine is at least in part suspended, by the traction of the serrefine at the point of anastomosis, is caused to assume a triangular form. Thus the lumen of the vessel is held open and less care is necessary to avoid accidental inclusion of the wall opposite to the point where suturing is being performed from being injured or included in the stitch.

The operator then, with the fingers of the left hand, grasps both ends of the fixing ligature previously held by the assistant, which has been knotted with the suture, and the assistant similarly grasps the two strands of the fixing ligature remaining free—that is,

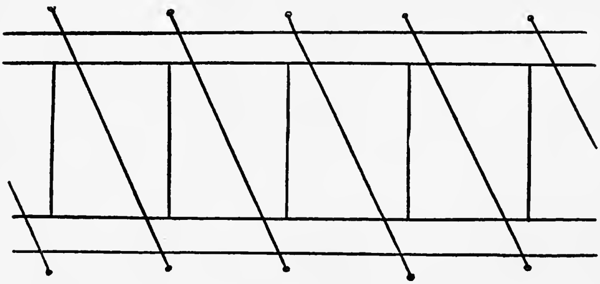

Fig. 32.—Diagram to show Direction of Continuous Suture on Outside (Oblique) and Inside (Transverse) of a Blood-Vessel.

the one placed in the left wall of the vessel—and the edges of the vessel between the ligatures are sutured by continuous stitching as before, and the suture is knotted to the ligature held by the assistant in the same manner as before practised. The strands of the ligature held by the operator are then released to a pair of serrefines, which may be taken from the posterior ligature. The ends of the fixing ligature held by the assistant are then grasped in the usual way by him, and by means of curved forceps he draws the end of the posterior ligature beneath the vessel to his side of the neck, and grasps it as he previously grasped the fixing ligature. The third and last line of sutures is then placed, and the suture knotted to the end of the suture held by the assistant. The suture and all the ligatures are then snipped off with keen scissors at a distance of 1 to 2 millimetres from the wall of the vessel. The outer loose coat on either side of the line of anastomosis is then gently stripped in the

direction of the line of anastomosis, which it may or may not cover, depending on the amount removed in the preparation of the vessel, the degree of traction on the vessel, etc. This completes the anastomotic operation proper.

The distal serrefine on the artery is now opened and the blood allowed to flow into the occluded portion of the vessel from the cephalic end. A little blood will escape from the needle holes on either side of the anastomosis, but if on examination of the entire circumference of the vessel at this point no considerable leakage, due to faulty approximation or incomplete drawing together of the cut edges, is observed, the serrefine is removed, and a dry cotton-gauze sponge pressed firmly over the point of suture. The serrefine on the central portion of the artery is immediately removed, and the full carotid pressure allowed to enter the vessel. The sponge is then cautiously raised and the line of union examined for free hæmorrhage. If none is observed, the sponge is replaced and light pressure on the anastomosis maintained for one minute. The pressure should not be sufficient to entirely occlude the lumen of the vessel, but it should be great enough to retard the circulation somewhat so as to favour the more rapid deposit of fibrin in the needle holes and crevices between the intimas of the two portions of the vessel. The sponge is then removed and the vessel presents a dry, smooth external surface, and the line of anastomosis is almost invisible. Should a little oozing yet occur the sponge is reapplied with gentle pressure until the leakage has ceased. In the event of a freely spurting point occurring, the index-finger of the left hand is inserted beneath the line of anastomosis, and the vessel raised somewhat and rolled on the ball of the finger until the leaking-point is brought uppermost. It is then carefully located, and a stitch placed so as to embrace the outer coats of the vessel on either side of the opening, and the suture tied so as to close the opening; or two or three continuous stitches are placed, and the ends of the ligature gently drawn upon so as to draw the tissues together, and the ends of the ligature cut off near the surface of the vessel, no tying being necessary. The loss of blood will immediately stop if the work has been done properly. If the escape of blood is so great as to interfere with correction of the defect, and if compression of the vessel central to the point with the ball of the thumb and the finger inserted under the vessel is inadequate the assistant then aids by compressing the vessel above with the right thumb and forefinger; or serrefines may be again placed upon the

vessel. In placing such stitches care must be exercised to avoid penetrating or injuring the opposite wall of the vessel with the needle, and it is for that reason that the intima is not to be included in the suture.

The vessel is now seen to be round and full and strongly pulsating. It courses obliquely across the trachea, from the right to the left side of the neck. Its colour will depend upon the degree of anæsthesia, so if the arterial blood is venous-hued it will present a bluish or purplish appearance, while if the blood is more nearly normal arterial it will be of a redder hue.

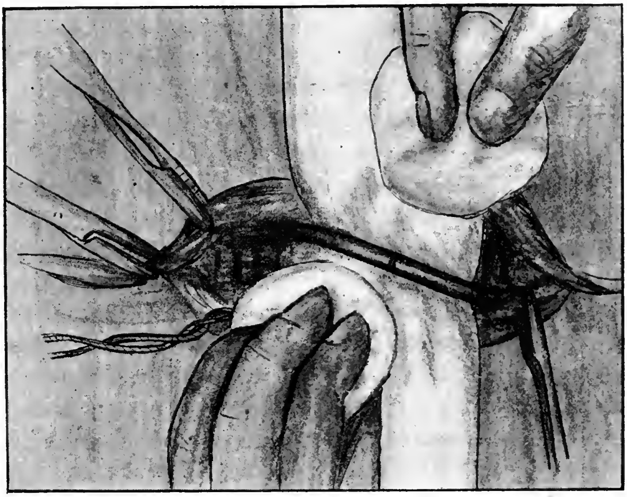

FIG. 33.—END-TO-END ARTERIAL ANASTOMOSIS SHOWN IN PRECEDING FIGURES COMPLETED, AND CIRCULATION RESTORED.

(Drawing from a photograph.)

The next step in the operation is the closure of the wound. This is done by means of a curved suture needle, bearing a single strand of medium-size catgut, which is tied into the eye to prevent unthreading. The wound is now wiped out, either with a dry sponge or one moistened in 0·9 per cent. sterilized sodium chloride solution ; but if the solution is used, all excess is removed by sponging, the tissues being left dry or only slightly moist.

Next the inner margins of the sterno-hyoid muscles are released from the retaining clamps and brought together. Beginning below, the edges of the muscles, including the dorsal aponeurotic tissue, are sutured together with the curved needle and gut. The first

stitch is firmly tied, leaving the free end of the ligature several inches long. The operator then grasps the free end of the ligature in his left hand and exerts sufficient traction upon it in the posterior direction to slightly stretch the tissues along the line of suture and bring them closely together in the mid-line. He then quickly sews the two edges together, using continuous sutures, placed sufficiently close to hold the tissues firmly and continuously together. When the first stitch after tying is placed, he releases the free end of the ligature to the left hand of the assistant, who continues the traction upon it as previously described. The operator pulls each stitch or each second stitch firmly into place, and while the succeeding stitch or pair of stitches is being placed, gentle tension is maintained with the left hand upon the ligature between the preceding stitch and the needle, but near the former in order that no slacking of the suture already in the tissue may take place; or such tension may be maintained by the right hand of the assistant. In any event, either the operator with his left, or the assistant with his right hand, depending upon the one that is free, grasps the tissues between the thumb and forefinger slightly ahead of the needle, and presses them firmly together from side to side, thus insuring evenness in the stretching and aiding the penetrating of the tissues by the needle by fixing them. When the last stitch in the anterior end of the suture line is placed, the remaining ligature is drawn through only a few inches, and the slack ligature between the last two stitches is doubled together and firmly knotted with the end bearing the needle. The ends of the suture are all then cut off within $\frac{1}{4}$ inch of the surface of the tissues. The anterior exposed tissues of the neck are then wiped with a sponge moistened with salt solution, after which the remaining unsutured tissues, divided by subcutaneous incisions, are stitched together in the mid-line as in the manner just described. The remaining exposed tissues to and including the edges of the skin are wiped with a sponge moistened with salt solution, and the side retaining clamps released. Using a heavier or more slowly absorbable gut, the skin is now sutured in the same manner, excepting that the stitches are placed more closely together and the clamps at either end of the incision

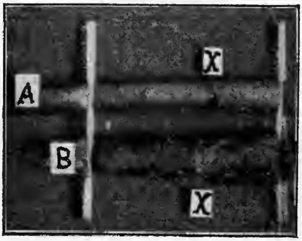

FIG. 34.—ANASTOMOSIS OF—A, ARTERY TO ARTERY; B, VEIN TO VEIN; SHOWING EXTERNAL SURFACE AT END OF OPERATION.

are removed. The line of union of the skin is now very firmly rubbed from above downward with a sponge well-moistened with alcohol. Any projecting subcutaneous tissue is thrust into the suture-line by means of blunt dissecting forceps. Excess of alcohol is removed, and the shaved surface of the skin sprinkled with powdered boric acid or iodoform, but preferably the former, and a thin pad of absorbent cotton, about 2 inches wide, applied over the line of skin suture. The anæsthetic has now been discontinued and the re-

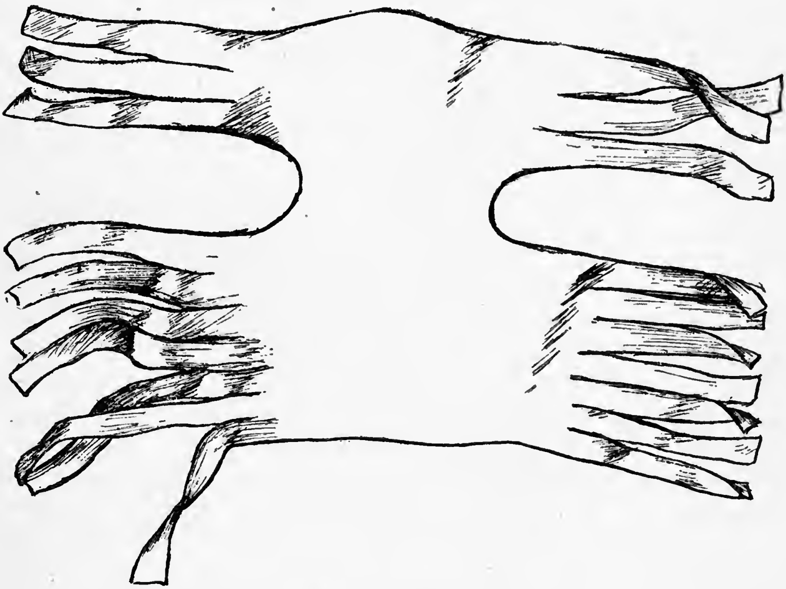

Fig. 35.—Tailed Bandage, forming Outermost Dressing for Neck or Trunk.

The rounded slots are for the fore-legs. Each pair of tails is knotted together over the dorsal mid-line, and adjacent ends of each pair are then knotted together. This form of bandage has been employed by the writer since 1903 with entire satisfaction.

mainder of the dressings are rapidly but carefully applied. These consist next of a thick pad of absorbent cotton of the proper length and width to embrace the whole of the neck, the lap being on the back of the neck. It is applied with the animal lying on its left side, the tapes having been removed from the wrists and ankles. A similar but heavier and somewhat larger pad of untreated cotton is next applied over the absorbent cotton, and it is long enough to encircle the neck two or three times. The cotton is now encircled with a firmly but not too tightly applied roller bandage, which is

fastened at two or three points along the dorsal mid-line with small safety-pins. A tailed bandage of suitable size should be at hand, but if such is not the case, one may be quickly made from a piece of heavy muslin. It is fitted over the dressing, and the ends of each pair of tails are tied in a single knot. After it is seen that the bandage fits snugly all over, and that it does not press too tightly at the edges, especially where it passes between the fore-legs, the knots are securely tied. The free ends of each pair of tails are then separated and laid in opposite directions, and each end is then firmly knotted with a member of the adjacent pair of tails on either side. When all are securely fastened, the ends are cut off within an inch of the knots, using heavy scissors kept for that purpose.

By thus knotting the ends of the tails together the dressing is made much more rigid and the divisions of the bandage are securely anchored together.

The dressing is now finished, and the nursing of the animal begins. At this time it will be coming out from under the influence of the ether, and before consciousness is fully re-established normal power of control of movements will be lacking, so it must be carefully watched to prevent its doing injury to itself. This may be done by having the attendant give his whole attention to the animal, it being placed on a dry, warm bed, in a well-ventilated but warm place, as by the side of the radiator in the preparation-room, several coarse sacks spread on the floor serving quite well for the animal to lie on. Another method, but perhaps not so good as the one above described, since the animal cannot be so closely watched, consists in placing the animal in a large, coarse-meshed bag, and suspending the bag so that it hangs freely in the air. Being unable to get a purchase on a fixed surface, the animal is unable to injure itself. After the animal has completely regained consciousness, which takes surprisingly little time in most instances, it is placed in one of the individual rooms in the hospital upon the raised screen bottom. A thick, soft cloth pad, which may consist of several coarse bags, is spread upon the screen bottom for the animal to lie upon, and a flat-bottomed vessel, partly filled with water, is supplied. The water vessel is set at some distance from the bed pad, preferably in a corner, in order to minimize the danger of accidental upsetting and wetting of the pad. No solid food is given until the following day, when the animal is again placed upon ordinary diet.

A properly applied dressing, such as described, will apparently cause the animal no discomfort, and it will wear for weeks without

adjustment of any kind ; but it is best to remove it after the wound is well healed, say in ten days to two weeks, after which the animal is removed to the permanent quarters. Should swelling of the lower jaw occur, the dressing should be examined closely, and if it appears to be too tight the bandages are to be slackened. A too snugly fitting bandage may be the sole cause of the swelling, especially if it presses too strongly under the surface of the throat near the larynx.

Coagulation of Blood.

Since the question of clot formation is so intimately related to the question of blood-vessel surgery, a consideration of the mechanism of coagulation as it is looked upon by modern physiologists must form a basis of any interpretation of phenomena of this class observed in blood-vessel anastomosis and other similar conditions.

Until a few years ago, fibrin—the appearance of which in blood is considered the essential phenomenon of clotting—was held by many to result from the action, under favourable conditions, of fibrin ferment upon fibrinogen in the presence of soluble calcium salt, an insoluble calcium-protein compound (fibrin), formed under the influence of the ferment. This conception may be simply shown by the following diagrammatic equation :

Fibrinogen + calcium + fibrin ferment = Fibrin.

Later investigations indicate that the processes concerned may be further isolated and studied, and that the rôle of calcium is different from that which is accredited to it by the older views. The present view of many physiologists is as follows :

Fibrin is formed from fibrinogen under the influence of fibrin ferment, even in the absence of calcium. Fibrin ferment is formed from a substance termed "thrombogen," which is derived from blood-platelets. Since it is known that blood-platelets occur in the blood within the blood-vessels (Osler), and that blood shed in ordinary ways contains few, if any, blood-platelets, it seems clear that the belief that the blood-platelets rapidly break up under what are recognized as favourable coagulative conditions—for example, the contact of blood with foreign or rough surfaces. Thus an abundant supply of fibrin ferment forming substance is automatically provided where needed—*i.e.*, at the point of hæmorrhage.

Under the influence of a substance termed "thrombokinase," thrombogen, in the presence of a solution of calcium salts, yields fibrin ferment. The substance, thrombokinase, is not a true

ferment, for it is itself used up in the reaction with thrombogen and calcium—that is, its action is quantitative. Such a substance is obtainable from most tissues of the body. The method usually employed is to finely grind the tissue to be tested and to extract the material thus obtained with water or diluted aqueous salt solution. In this way evidence has been obtained that different tissues exhibit evidences of differences in richness of the substance; but most tissues apparently contain a sufficient amount to insure coagulation of blood coming in contact with their surfaces after injury to them. Another source of thrombokinase is white blood-corpuscles; and perhaps blood-platelets themselves yielded a certain amount of the substance by their disintegration. It is stated that the white blood-cells in man do not suffer complete disintegrative changes when blood is shed. But it cannot be assumed that they do not liberate such substances under such conditions, and it is known that they are relatively rich in thrombokinase.

The reaction resulting in the formation of fibrin ferment may be represented diagrammatically as follows:

Thrombogen + calcium + thrombokinase = Fibrin ferment;

and the reaction resulting in the formation of fibrin thus:

Fibrinogen + fibrin ferment = Fibrin.

Howell states that thrombin probably does not act upon fibrinogen after the manner of an enzyme. Increasing amounts of thrombin give increasing amounts of fibrin, although in decreasing proportions. He further states that pro-thrombin may be converted into thrombin in solutions free from calcium salts.

In addition to the above outline, which, though brief and incomplete, presents the major current conceptions of the mechanisms of blood coagulation, a brief résumé of certain factors that are known to accelerate or to retard coagulative processes will be given in order to facilitate the presentation of the consideration of coagulation in relation to vascular suture.

It has been held for a very long time that if a segment of blood-vessel, such as an external jugular vein, be ligated at either end, and removed from the body, the blood contained therein will remain fluid almost indefinitely. If after a time the segment is opened and the blood permitted to come in contact either with an injured portion of the tissue—that is, a portion not covered with unruptured endothelium, or with any other foreign surface, even the air—coagulation will be induced. The explanation of these phenomena seems

to be that so long as the blood is in contact with intact vascular endothelial surfaces only, the fibrin ferment factors, thrombogen and thrombokinase, are but slowly liberated from the formed elements from which they are derived. So the clotting tendency is not so rapidly developed as when blood comes in contact with foreign surfaces.

The nature of the foreign surface is important in determining the rate with which blood will clot. For example, a raw tissue surface not only acts as a foreign surface in causing disintegrative changes in the organized elements that supply ferment factors, but itself contributes thrombokinase. Thus we have an illustration of an automatic protective mechanism devised by Nature for controlling hæmorrhage. Other foreign surfaces, inert in the sense of actually contributing a ferment factor, vary greatly in their property of hastening the coagulation process. In a measure this is due, apparently, to the ratio of actual surface to unit of blood. For a roughened surface is said to hasten coagulation more than a smooth one ; but the nature of the substance presenting the surface appears to be a factor, as it is commonly stated that under otherwise similar conditions blood in contact with an oiled surface will clot more slowly than blood in contact with an unoiled surface.

Some of these facts have been made use of by surgeons almost from time immemorial. For example, a very old remedy for controlling hæmorrhage was to apply cobwebs, earth, or lint to the wound, and to-day the troublesome oozing from the diploë of the cranial walls is sometimes controlled by the application of some fibred material, such as cotton. And in transfusing blood oil-coated tubes are employed.

In operations upon blood-vessels it is obvious that conditions leading to the formation of occluding thrombi must be avoided if patency of the lumen is to be preserved. Therefore no manipulation of the vessel is practised that may jeopardize the result through injury of the intima, and it is for this reason that overstretching or handling with forceps, which might rupture or crush the intima, is avoided ; and it is for the same reason that extreme care is necessary in applying the instruments by means of which temporary occlusion is produced ; and it is for similar, though not identical reasons, that after temporary occlusion and section of the vessel the blood within its lumen is removed as rapidly and completely as possible —that is, clotting is avoided in order not only to prevent the occurrence of an excessive amount of fibrin ferment within the

vessel, but to avoid the possibility of fibrin being present within the vessel after the operation is completed. For it is known that intravascular clotting may be produced by the introduction of fibrin ferment in sufficient amount into the circulation; and that the presence of fibrin within a vessel is prone to lead to thrombus formation, for it not only acts as a foreign body, but it has the curious property of absorbing or otherwise attaching to itself a relatively large amount of fibrin ferment, though the latter, as before pointed out, is not considered as a structural constituent of fibrin. So it seems logical to remove the blood before much fibrin ferment is formed and before fibrin is laid down, for the reasons given and for the reason that fibrin is much more difficult to remove than the unclotted blood.

By thorough sponging of the cut surface and lumen of the divided vessels, not only is the blood effectively and safely removed, but juices from the cut tissues are also removed. Further, the application of a thin coating of oil serves the function of covering over, or in a way sealing up, the raw surface, thus tending to render it less able to subsequently favour fibrin formation; but in addition to this, oil thus applied not only facilitates the suturing by weakening the cohesive power of the vessel for the ligature, but protects the tissues from drying during their exposure to the air. This is an important consideration, and it becomes of graver magnitude when small vessels are operated upon. It should be remembered that oil itself is not wholly devoid of action on the tissues, and for that reason it should be used in moderation; but when properly used, as the algebraic sum of its action is benign, it should be dispensed with only after careful study. It is obvious that in very humid air the drying factor decreases in seriousness, and that the degree of drying during a short operation is proportionally less than during a longer one. So in this respect the optimum conditions are fulfilled when the operation is rapidly performed in a moisture-ladened atmosphere, and a minimum of oil used. I may say that under the first two conditions just mentioned my own inclinations would be to dispense with the oil entirely; but since successful results are achieved in slow operations, and when oil is abundantly used—that is, from the standpoint of securing a good functional result so far as the circulation is concerned—the operator entering this field should not dispense with the oil until he has satisfied himself that he has arrived at the point where he can practically control the result by his skill and speed.

The employment of salt solution upon cut edges of the tissues or inside the lumen of the vessel is not recommended, for it tends to contaminate the lumen of the vessel with tissue juice; it is not altogether without harmful action on tissues; and since excellent results are obtained by the method already described for freeing the vessel of blood, it unnecessarily complicates the technique and lengthens the time of the operation; besides, it tends to make the wound sloppy. So it is recommended that its use be restricted to the outer surface of the vessel, if its use seems necessary to prevent undue drying, and to its application to the other tissues exposed during the operation. Used for these purposes, it is best applied with a moistened, but not a dripping, sponge. Its further use is discussed in the division on technique; and the reason for the view that it is not without harmful action is stated in the division on the preservation of vitality of tissues (p. 115).

But to emphasize these points, it may be said that the best preservation of normal macroscopical and microscopical structure has been observed in the most rapid operations, and with the minimal use of oil and salt solution. And this must be so even if experimental proofs were lacking, for normality of structure depends upon normality of conditions, and exposure and manipulation of blood-vessels, and their treatment with oil and salt solution, are abnormal conditions. And since this is not a consideration of the degree to which blood-vessels may be exposed to abnormal conditions without losing their normal structure and functions, but a consideration of measures devised for the purpose of permitting operations upon blood-vessels with the minimal alteration of normal conditions, discussion need not be further pursued.

Considering now, from the coagulation standpoint, the line of approximation of the divided edges of the vessel and the presence of the suture within the lumen, we are able to introduce some interesting observations that go a long way toward explaining the experimental findings—that is, the very excellent preservation of anatomical structure, including patency of the lumen.

If the ends of a divided blood-vessel be sutured together, and then a segment of the vessel bearing the anastomosis be immediately cut out and laid open longitudinally, which may be quickly done by means of a pair of small scissors, the condition of the intimal surface at the point operated upon can be studied. In a perfect operation a narrow transverse area is seen. It is limited on either side by the needle punctures which are themselves connected by the stitches

lying in grooves, which gives the band-like suture area a corrugated appearance. The thread appears to fill the needle holes, but its surface is exposed to the lumen of the vessel as it passes across from hole to hole. The junction of the intimal edges is to be seen as a transverse line, but little if any raw surface is exposed. In a way, the intimas present an appearance of being matted together. Of course, no knots are visible, as they are invariably tied on the external or adventitial surface of the vessel. On the whole, the anastomosis presents a smooth though somewhat corrugated or puckered appearance, from the intimal surface, which is marked across by the stitches which lie in shallow grooves, due to the pressing of the material into the yielding intimal tissue by traction upon the thread during the operation. The semi-circumference of the stitch material crossing the suture zone is entirely exposed to the lumen of the vessel.

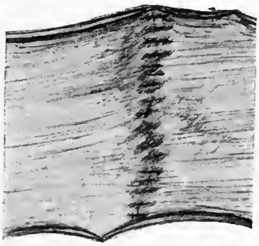

Fig. 36.—Appearance of Intimal Surface of Anastomosis Two Hours after Union of the Ends of Divided Arteries.

(Observed at distance of 1 yard.)

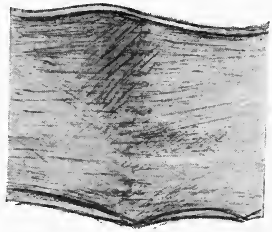

Fig. 37.—Appearance of Intimal Surface of Anastomosis Twenty Days after Union of the Ends of Divided Arteries.

(Observed at distance of 1 yard).

With a lens it is usually possible to observe that continuity of the intimal surface is not so complete or perfect as the grosser examination indicates, as roughened intimal margins and even small gaps may be observed along the line of approximation of the intimas, and many or all of the needle holes, particularly on the sides away from the suture field, show raw areas and surfaces. The intimal surfaces of the stitches are seen to lie snugly in the grooves already described.

Now, it would seem that here we have favourable conditions for fibrin deposition, foreign surfaces—*i.e.*, surfaces capable of yielding thrombokinase—the raw tissues of the vessel walls exposed by gaps on the intima, and the stitches, rendered more or less inert so far as inducing the deposition of fibrin is concerned, by impregnation with oil, but certainly not without some action in this

direction. It is true that the total area of such foreign surface does not seem very great relative to the whole intimal area, but it could not be predicted with certainty, from the facts thus far stated, whether or not an occluding thrombus would occur.

So after predicting the laying down of fibrin, at least on the raw surfaces, we turn to actual experimental findings for the answer to the main question—viz., preservation of patency of the vascular lumen. Considering the results of such examinations as described, only taking the segments at intervals of days and weeks after the operation, one finds that fibrinous deposits are laid down at least on the raw surfaces; but such deposits are relatively slight, and they very soon undergo resorptive changes and become protected with an intimal-like covering. The exposed threads are also quickly covered over with a similar coating, so that if examined with a lens the whole intimal surface appears to be continuous.*

Since this shows that the coagulant action of the blood has been exhibited, but, happily, in what may be considered only a benign way, we may conclude that the technique, though imperfect from the standpoint of avoiding the setting into activity of the coagulating property of the blood—is satisfactory from the practical standpoint—namely, the avoidance of the formation of an occluding thrombus, or a thrombus of size sufficient to embarrass the circulation through the anastomosis.

The somewhat peculiar nature of the fibrinous deposits in the interstices of the intima as described is more fully discussed in the division on results (p. 106).

So the occurrence of clotting in the manner described, and of the nature to be later considered, is regarded as a regular phenomenon of blood-vessel suture. It is looked upon as favouring the union of disrupted endothelial surfaces, for it acts not only mechanically to close all minute openings through which blood might escape, but it quickly results in causing the endothelial surface to present a continuous, smooth, inert surface to the blood, thus restoring approximately the conditions of a normal blood-vessel.

The mechanism limiting the extent of such fibrinous deposits is not clearly understood. But consideration of the reaction produced by introduction of fibrin ferment into the circulation

* In a recent experiment eleven common carotid arteries and eleven jugular veins of dogs were pierced transversely with from one to twenty-four strands of silk. In some of the experiments the threads were oiled, and in some they were untreated. Three weeks later the vessels were examined, and none were found to be occluded.

is of interest—namely, the increase of antithrombin in the blood. It is commonly held that the liver is intimately concerned in this reaction. But be this as it may, it would seem that following blood-vessel suture, since a clotting-like action occurs, and it is possible that some fibrin ferment is formed that passes off into the blood-stream, a similar reaction may be induced. But the amount of ferment absorbed by the blood is probably very small, as the mass of the clot-like formation is slight, and fibrin is known to bind fibrin ferment in a curious manner, since it is not believed to be a chemical union. And therefore such reaction is probably too small to be detected by present experimental methods. So the formation of anticoagulant substances in this manner would seem to be a possible, though not very powerful, factor in limiting the clotting that occurs in the field of suture. Experimental observations confirm this view. For, in general, it may be stated that the magnitude of such thrombus formation apparently varies indirectly with the circulation—*i.e.*, the mass of blood per unit of intimal surface. This might be interpreted as being in favour of the anticoagulant view by supposing that, if a small increase in this property were induced by fibrin ferment as described, under conditions where the amount of blood passing over a unit area of internal surface was large, the anticoagulant action would be enhanced by the exposure of the injured surfaces or thrombus-covered surfaces to a greater quantity of blood—hence a greater quantity of anticoagulant substance would act upon a given area in a given time. But the character of the thrombi and a consideration of the mechanism of coagulation indicate that other factors are perhaps of greater importance. In brief, the thrombi are of the lamellar white type. Preceding their appearance, it is probable that the platelets and white corpuscles coming in contact with the raw surface, which, indeed, may actually attract them, or cause them to accumulate as by an agglutinative process, are so altered that the essential fibrin ferment pro-substances, thrombogen and thrombokinase, are liberated. And since calcium is present, fully formed ferment quickly appears at the site of injury. Direct coagulative processes then follow, and the raw surface is soon buried. That an adhesive mechanism exists is indicated by the gathering of the white blood-cells and platelets at the point, and by the clinging to the raw surface of the thrombus itself. But the nature of the process is not understood.

It seems reasonable to suppose that the degree of injury suffered

by a blood-cell through contact with a foreign surface will within limits vary with the period of exposure. And since it is through injury to the cells that the pro-fibrin ferment factors are liberated, the amounts of these will vary in the same way. If this is so, then it follows that a blood-platelet or white corpuscle would be more exposed to a given surface in inverse proportion to the speed with which they are carried ; and that degree of injury, hence amount of pro-ferment factors liberated, will likewise vary with the circulation. Further, the number of blood-platelets or white corpuscles in proportion to the mass of blood passing through the vessel which come directly in contact with the wall varies indirectly with the diameter of the blood-stream, and therefore the tendency for coagulation per unit mass of blood will, from this standpoint, be greater in a small one.

But since the same sizes of needles and threads are used for vessels in the smaller class, which individually vary greatly in size, not only are the needle punctures and stitch trauma proportionately greater collectively in the smallest vessels, but individually as well.

To sum up, we may conclude that a large number of factors may concern the question of coagulative processes, and the limiting of such processes, many of which are little understood even when considered singly. So how complicated the problem becomes when they are considered collectively, and a prognosis of the result of a specific intimal injury attempted !

To simplify the conception of the relations of the more important factors concerned, the following standpoint is taken by the writer : Thrombus formation after intimal injury, or the introduction of a foreign body into the lumen of a blood-vessel, as a suture, will vary directly as to (1) the ratio of injured or foreign surface to the diameter of the lumen of the vessel ; or (2) the degree of cupping or pocket formation at the abnormal point ; (3) the coagulability of the blood. And it will vary indirectly as (1) the diameter of the vessel; or (2) the amount of blood passing the point in a given time ; and (3) the velocity of the blood—*i.e.*, as the ratio of unit mass of blood to endothelial area.

Exact values of these factors or methods of determining them in most cases are wanting, so it is impossible to express by an exact formula the ratios existing when thrombus formation proceeds beyond the desirable degree. But perhaps it is not wholly hopeless to desire such a state of knowledge.

Neither general nor local specific anticoagulant agents, such as leech extract (hirudin), have been employed. For successful results are easily achieved as described, and whether such restraint of coagulation would be on the whole desirable is doubtful. A certain amount of thrombus formation is highly desirable for the temporary repair of the blood-vessel, so no leakage will occur; and it would be undesirable to diminish general coagulability on account of the danger of the difficulty that would ensue in securing a "dry" wound.

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CHAPTER III

OPERATIONS UPON BLOOD-VESSELS

In the section devoted to a detailed description of operative technique, direct end-to-end anastomosis of two ends of transversely divided vessels was chosen as being a representative operation. And much of the procedure described is applicable to any operation involving the suturing together of the walls on any blood-vessel in which the lumen is opened. In certain operations, however, some of the manipulations are not practised, and certain other procedures are carried out. So the common operations will be described in order that essential differences in technical procedures may be considered in relation to their actual application, and also for the purpose of indicating by concrete examples the extent to which blood-vessels may be operated upon with good functional results as regards institution, restitution and preservation of free circulatory channels.

The simplest class of operations deal with the repair of wounds in the walls of blood-vessels, either arteries or veins. In general this is best accomplished by freely exposing and temporarily occluding the vessel on either side of the point of injury, and stitching the edges of the wall together by means of a continuous suture, in much the same manner as described for the closing of leaks in an imperfect end-to-end anastomosis (p. 49). If only a few stitches are required, and if they can be quickly placed, the blood within the segment of vessel temporarily shut off from the circulation need not be considered; but if several minutes must elapse between the shutting off and the restoration of the circulation, the excess of blood must be removed, as even moderate coagulation within the vessel, for reasons already stated (p. 56), very seriously jeopardizes the result aimed at. The blood may be removed sufficiently well by the stripping and sponging technique—that is, the vessel is compressed on both sides of the injury between the balls of the thumbs and

index-fingers placed close to the temporary hæmostatic clamps, and by gentle, and two or three times repeated, stripping movements carried to the injury, the blood is pressed out of the vessel through the opening resulting from the injury and absorbed by a dry cotton-gauze sponge, held tightly against it. Or if for any reason this is not feasible, one of the clamps employed for temporary shutting out of the circulation may be released sufficiently at minute intervals to permit sufficient blood to enter to displace the stationary blood contained in the lumen, thus, by a process of displacement and refilling, to permit no blood to remain in the segment for coagulation to take place. But the method of removing the blood is much the more desirable. The edges of the wound should be trimmed slightly if too ragged. This may be conveniently done by grasping both edges of the lips of the wound with the tips of the blades of a pair of round-nosed dissecting forceps, and while stretching the walls outward by gently applied traction on the forceps to snip off the edges with a single clip of a pair of small, keen scissors held longitudinal and parallel with the surface of the vessel. Whenever possible, and when the resulting stenosis will not be too great, scissors are used, not only because the amount of tissue removed can be very accurately gauged, but because both sides of the wound will be counterparts—a very important feature in all plastic work. Scissors with curved blades are excellent for this purpose. The reason for making a longitudinal cut with the scissors is that less tension will be exerted on the suture after the wound is closed. Of course, some constriction of the lumen is inevitable, but by exercising care to save all of the sound tissue possible, the chances are that in simple injuries this factor will not be appreciable, as the lumen of a blood-vessel may be considerably narrowed permanently without imperilling the function of the tissues supplied by the vessel through circulatory failure (see p. 142).

After the margins of the wound have been prepared—and too much emphasis cannot be laid upon the desirability of avoiding removal of more tissue than is necessary to give regular edges for suturing—the lips are brought together by pressing the vessel between the ball of the left thumb and forefinger, so that it is flattened and the raw edges of the wall appear on one edge, and are stitched together by a continuous suture. Beginning at one end, the first stitch is placed about 1 millimetre back from the end of the wound; it extends through both walls, but barely penetrates

the intima. It is drawn well through, and the two ends doubly knotted firmly against the external surface of the vessel. The remainder of the stitches are similarly placed along the margins of the lips of the wound, penetrating the coats of the vessel about $\frac{1}{2}$ millimetre from the raw edges of the lips, and being placed at intervals of about the same distance. Each, or every other, stitch

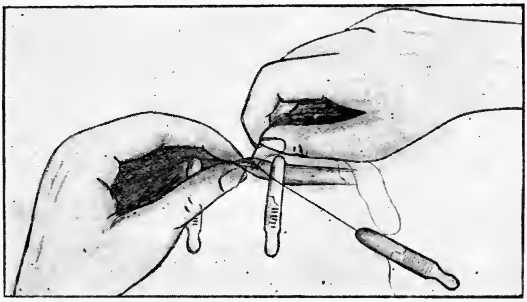

FIG. 38.—REPAIR OF LONGITUDINAL SLIT IN BLOOD-VESSEL WITH FINE CAMBRIC OR LACE NEEDLE AND THREAD, SHOWING POSITION OF HANDS.

is gently but firmly drawn until all slack is taken up and the endothelial margins are firmly and continuously approximated. When the extremity of the wound is reached, a last stitch, corresponding to the first, is placed, and the end of the suture tied in precisely the same manner as in sewing a skin wound (p. 51). In fact, the technique for thus sewing together the edges of a wound in a blood-vessel differs only from that described for the skin in the nature and

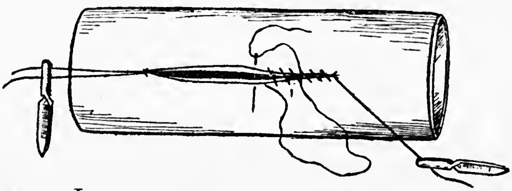

FIG. 39.—REPAIR OF LONGITUDINAL INJURY IN A BLOOD-VESSEL BY MEANS OF CONTINUOUS THROUGH-AND-THROUGH SUTURE, SHOWING MANNER OF STITCHING.

delicacy of the needle and suture material. The operation is concluded by snipping off the ends of the suture close to the vessel and restoring the circulation by removing the temporary hæmostatic clamps, and observing and treating the line of suture as in the case of end-to-end anastomosis.

In the case of small, more or less circular openings, the few

stitches necessary may be placed without tying the first one, and the ends tied above the stitches collectively. And with such small wounds it may be possible to pick up the vessel on the ball of the index-finger, and to close it without other manipulation—*e.g.*, as described for repairing a fault in an imperfect end-to-end anastc-

FIG. 40.—REPAIR OF TRANSVERSE SLIT IN BLOOD-VESSEL WITH FINE CAMBRIC OR LACE NEEDLE AND THREAD, SHOWING METHOD OF HOLDING VESSEL ON FINGER.

mosis (p. 49). Thus the damage may be repaired without producing temporary hæmostasis by means of clamps.

Quite recently an ingenious clamp for temporarily isolating and shutting off the blood from an injury in a vessel, but which permits the circulation to continue through the restricted lumen, has been devised and described by Professor Stewart. As shown in the figures (p. 68), the essential features of the clamp are as follows:

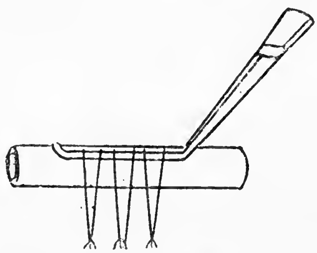

FIG. 41.—JOANI'S CLAMP APPLIED FOR SHUTTING OFF THE CIRCULATION TO A PORTION OF THE WALL OF A BLOOD-VESSEL.

The long, narrow grip of the jaws on the longitudinal direction. The grip is narrow in order that as little as possible of the lumen may be encroached on. The extension of the grip at each end, at right angles to the length of the vessel, is necessary to complete the occlusion of the isolated segment. The length of the rectangular portions should be proportioned to the diameter of the vessel worked with. If too long, they project too far beyond the vessel and thus make the field of operation less accessible for some purposes. The size of the hollow beyond the gripping edges must be great enough

to accommodate the non-occluded part of the vessel without occluding it.

As pointed out by Professor Stewart, such clamps might be employed to arrest hæmorrhage from a wound in a large vessel, which could not be clamped completely without detriment, and during the suturing of the wound; possibly in the treatment of sacculated aneurism in some situations; in performing lateral anastomosis of blood-vessels in cases where it is undesirable to completely occlude one or both of the vessels for the time required in the operation; in performing lateral implantation of one vessel on to another which must not be totally occluded; in inserting a cannula laterally into a vessel without stopping the circulation, when there is no convenient branch of the vessel which might be used, or when it is disadvantageous to occlude such a branch; in narrowing experimentally the lumen of a vessel without temporarily occluding it, especially when a diminution of the lumen by a definite amount is desirable.

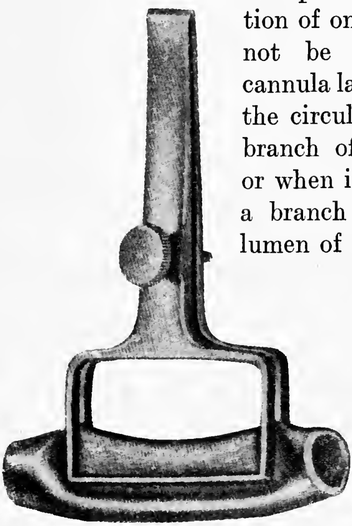

Fig. 42.—Clamp to be applied to the Wounded Side of the Vessel only. (Stewart.)

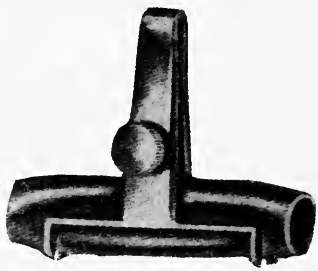

Fig. 43.—Form of Clamp with a Screw for graduating the Pressure. (Stewart.)

The complete temporary shutting off of the circulation in certain tissues is open to very grave objection, for it is known that certain tissues are exceedingly susceptible to temporary anæmia, and irreparable injury may thus be produced. This is true especially of the brain. But a relatively small amount of blood may suffice to maintain even the brain in such a condition that good return of function is possible with restored circulation after considerable periods of profound though incomplete anæmia (Hill). But, fortunately, owing to collateral circulatory channels, even such

vessels as the descending aorta may for a time be completely occluded without serious permanent derangement of function of the tissues thus temporarily deprived of much of their blood-supply; indeed, surprisingly slight derangement of function, after comparatively rapid and complete occlusion of the abdominal aorta just posterior to the renal arteries, has been observed by the writer. The animal was a cat (p. 244, Cat 32). The aorta was pletely occluded both above and below the renal arteries for twenty-five minutes. Owing to bungling manipulation, particularly of a trocar thrust into the aorta just posterior to the renal vessels, the vessel was very severely injured. For a period of several days following the operation some paralytic symptoms were noted in the hind-quarters, but these disappeared completely. Twenty days after the operation the animal was chloroformed, and at post-mortem examination the aorta was found to be completely occluded by an organized thrombus, situated just posterior to the renal vessels. Now, all the facts in this case indicate that the aorta became completely occluded within a comparatively brief period after the operation. Yet the condition gave rise to only moderate and temporary derangement of function. One striking feature of the results, though not bearing directly on the major problem, may be mentioned—viz., the result of injury to the aortic intima. In two cases only have we observed occluding thrombi in the aorta, and in both cases the result was due to gross fault in technical procedure, by which not only the intima, but the outer walls of the aorta, were crushed and otherwise maltreated. In one case the thrombus extended for some distance both above and below the origin of the renal arteries, and the cat died during the first day.

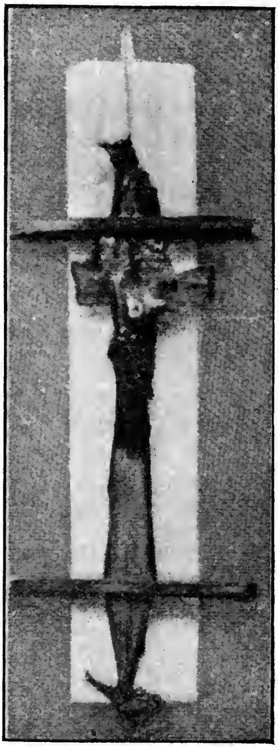

FIG. 44.—AORTA OF CAT 32, SHOWING OCCLUSION BY THROMBUS JUST POSTERIOR TO RENAL ARTERIES.

Kidneys perfused with salt solution, January 26. Cat killed February 15.

(*Archives of Internal Medicine*, 1910, v. 232.)

Similar observations on the effects of aortic occlusion have been

made, and the literature, which has been reviewed by Halstead, who himself has made numerous experiments and observations, is fairly voluminous (p. 143). In view of this it is well to be careful in drawing conclusions as to patency of lumen after operations upon blood-vessels from lack of, or disappearance of, symptoms attributable to occlusion of the vessel. A case in point is that of Braun, who resected a segment of the abdominal aorta of a child and sutured the ends of the vessel together. Twelve days later the child was in good condition, and the inference has been drawn that the operation upon the aorta itself was successful; but though this might easily be true, it by no means follows from the observation. For occluding aortic thrombosis might occur; the clinical observations would be the same as those reported.

It is safe to say that when patency of the lumen of a blood-vessel can be preserved, even though the lumen is greatly decreased in size, it is better to repair it by suturing than to ligate it. For even though the circulation may for a time be inadequate for the normal nutrition of the tissues supplied, they may be tided over the period necessary for an adequate circulation to become established through collateral channels, and the tissue may then be able to recover and assume its full duties.

In the event that so much of the vascular wall is missing or has to be removed that preservation of patency of the lumen becomes a matter of grave doubt, then one has the choice of four things —viz., ligating on either side of the injury; restoring the vessel wall by means of a patch; dividing the vessel transversely on either side of the wound and directly anastomosing the ends; or, after removing the injured segment, to interpose a segment of another blood-vessel or similar tubular segment and restoring the continuity of the vessel by anastomosing its ends to the ends of the vessel.

Ligations may be safely practised upon vessels of secondary size and importance, as, for example, the ulnar artery. Here the parts supplied have very abundant anastomotic connections, so ligation of the artery mentioned will produce little alteration of the blood-supply, as the anastomotic channels will quickly become adjusted to the increased demand made upon them. As an example of an intermediate type of vessel, the brachial artery may be mentioned. Ligation here is much more serious, and though care be taken with such vessels to preserve to the greatest extent possible all branches which from their position, size, and distribution are the most important in the establishment of an adequate anasto-

motic circulation, less perfect results can be predicted with certainty. Of the more extreme type, the renal artery is a good example, for when, as in the majority of instances, the kidney is supplied with but a single main artery, shutting off of the circulation through the vessel is surely followed by profound disturbance of function of the organ; and notwithstanding that the kidney receives some blood through other vessels (particularly by way of the ureter) this is so meagre that the organ will undergo extensive degenerative changes after the renal artery is tied. But it is well to bear in mind that not infrequently the kidney is supplied by more than one renal artery (see p. 200). In such a case the tying of one trunk would be a different matter.

Another example that is of particular interest, in view of the somewhat divergent views expressed as to the results after ligation, is the common carotid arteries. It is commonly held by surgeons that in man ligation of even a single common carotid artery is a grave procedure owing to the danger of serious derangement of the blood-supply of the brain. An examination of the literature on this subject does not bear this out from anatomical and experimental physiological standpoints; for, though a relative difference in the blood-carrying capacity of the cerebral arteries of different animals and the relation of blood-supply to cerebral activity is admitted, yet, since what may be termed the secondary or reserve or anastomotic circulatory channels are at least not markedly restricted in the morphological sense, it is rather surprising to the experimentalist that such a difference exists in man as compared to lower animals, for both common carotid arteries may be permanently ligated at the same time in many of the lower animals, with the production of scarcely any objective symptoms, or none at all. The brain is exceedingly susceptible to alterations of its blood-supply, yet the writer has completely occluded, by direct compression, both common carotid arteries in man for a period sufficient for the removal of the whole of the lower jaw, the object of the arterial compression being the control of hæmorrhage, which was very successfully accomplished, and yet the minutest observation failed to reveal any evidence of inadequacy of cerebral circulation. The patient, though unconscious from ether, was not in a deep stage of narcosis, and such eye reflexes as were present were not visibly diminished by carotid occlusion, nor was there any marked change in respiratory rate, and no post-operative symptoms attributable to the compression of the carotids were observed

through the brief period over which observations extended (*cf.* p. 149). Notwithstanding this, it is known that simultaneous compression of both common carotid and both vertebral arteries in similarly anæsthetized cats or dogs is quickly followed by marked evidences of inadequate cerebral circulation—viz., disappearance of ocular reflexes, dilation of the pupils, and cessation of respiratory movements; while carotid compression alone gives slight or no evidence of such a condition (p. 315). The writer does not stand alone in the view that the carotid arteries may with safety be compressed, for Professor Hill, after much experimentation and study, stated that in his belief, if gradually occluded at intervals, both carotids and both vertebral arteries might be safely tied in man. He mentions a case of practically complete occlusion of these four arteries in man by a pathological process, without ill effects. Hill emphasizes the importance of gradual compression of the arteries to avoid unfavourable results.

But in order to avoid the possibility of being misunderstood, I will state that, though present experimental evidence does not speak against either temporary or permanent occlusion of the common carotid arteries, yet, owing to contradictory clinical observation on man after permanent occlusion of even a single common carotid artery, the question must be considered as not settled, and therefore all considerations must be carefully weighed before practising such occlusions on man. As a precautionary measure it is suggested that, when ligation is definitely decided upon, it would be well to temporarily compress the artery for a period, and to very carefully observe the results upon the eye reflexes, discharge of the respiratory and motor centres, or other manifestation, before permanently fixing the ligature. For from what is known it would seem that if no objective symptoms were produced by the temporary occlusion, the occurrence of symptoms after permanent ligation would be less probable than if symptoms were observed in the first instance (see p. 150).

Restitution of the vascular channel by laying a patch in the opening made by injury is feasible; but excepting for experimental purposes, it will probably be rarely employed; for, in addition to being a more complicated and difficult method, it is employed only in such cases as may not be successfully handled by simple suture of the edges of the wound directly in so far as restitution of patency of the lumen is concerned. So the indication for its employment narrows to a consideration of those cases where constriction of the lumen

occurs, which necessarily follows repair by simple suture when portions of the vascular wall are actually missing or have to be removed, in which the effect of narrowing of the lumen upon the subsequent functioning of the tissues affected is serious. For example, in the case of an injured vessel which supplies a tissue whose resistance to poor circulatory conditions is weak, and is poorly supplied with anastomotic blood-channels, and therefore may be seriously affected by constriction of the artery, it would probably be better to patch the artery in order to retain a lumen of adequate size. But since the danger of serious thrombus formation will be greater in patching than in simple closure of the wound, owing to the relative increase of foreign surfaces in proportion to the diameter of the vessel, other considerations must enter into the final decision, as the removal of a partial or complete segment of the artery bearing the injury and direct suture of the walls, or complete removal of a segment and the interposition and suture of a suitable tubular segment between the

Fig. 45.—Showing Segment of Vein interposed between and sutured to the Ends of a Divided Artery.

ends. All factors must be as carefully considered as possible in each individual case, in order that the operation offering the best chance of success may be selected.

In case the injury is so extensive as to necessitate the removal of a complete segment of a vessel, vascular continuity may be restored by direct anastomosis of the ends, which can be accomplished by following the technique already described. But if much tension is necessary to bring the ends together, either through the removal of a long segment or the retraction of the ends of the vessel after division, it is best to employ a suitable tubular segment to restore the circulatory channel. An ideal segment for this purpose would be one from the same artery, but as this is not practicable, then such a segment from a similar animal or from a different species of animal, or a venous segment from the same animal, may be employed. The segment selected should be of about the same size as the artery, and it should be cut of a length

equal to or a little greater than that of the segment removed, so that when the continuity of the vascular channel is restored there may be no very abrupt change in the size of the lumen nor in the length of the vessel.

As a full discussion of the sources of such materials available for such purposes, together with a consideration of methods of preparing and handling, is presented in another place (p. 129), only the technique of the operation will be considered here. After the segment is prepared by cutting to the proper length and freeing the ends of excess of loose outer tissue, it may be lightly coated with oil, and placed in position between the ends of the vessels to be reunited. These ends having been prepared in the manner described for a direct end-to-end anastomosis, and the floor of the wound covered with a strip of oiled silk or other suitable waterproof material of proper size, the ends of the divided vessel are laid in a line, and the segment placed end-to-end with them. In case a segment of vein is employed, owing to the possible presence of valves, it is desirable to place it so as to preserve the normal direction of blood-flow through it. Each end is then in turn fixed to the corresponding end of the blood-vessel, whose continuity is to be restored, by the three fixing ligatures already described (p. 44), and the ligatures are tied. Then in turn each anastomosis is completed in the

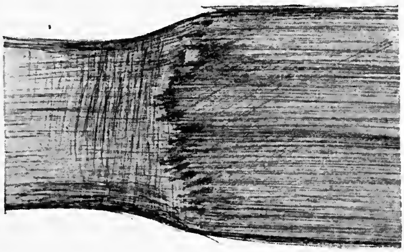

FIG. 46.—APPEARANCE OF INTIMAL SURFACE OF ANASTOMOSIS TWENTY-FOUR HOURS AFTER UNION OF THE ENDS OF DIVIDED ARTERIES OF UNEQUAL SIZE.

(Observed at distance of 1 yard.)

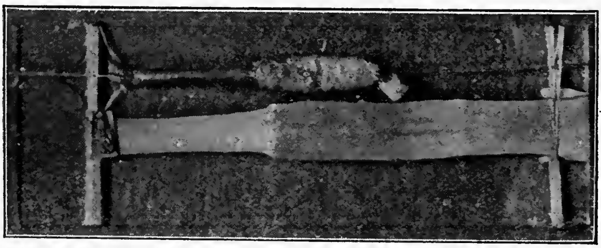

FIG. 47.—UNION OF ARTERIES OF UNEQUAL SIZE, ADVENTITIAL AND INTIMAL SURFACES, ONE DAY AFTER OPERATION.

usual way, the circulation restored, and the operation finished as in the case of a simple anastomosis. Any branch on the segment not previously ligated is tied close to its mouth, using a small silk ligature for the purpose. By this method large vascular tracts may be removed, and satisfactory re-establishment of the channel accomplished.

The operation of direct end-to-end anastomosis of arteries has been sufficiently described for vessels of similar size (p. 44). In the case of thus uniting the ends of two vessels varying considerably in size it is necessary in sewing the edges together to uniformly take longer stitches in the edge of the larger vessel in order that the excess of wall may be evenly distributed around the entire circumference of the line of suture. When this is properly done, vessels of very unequal size may be very satisfactorily united. (Figs. 46 and 47.)

What has been said of arteries is true also of veins. The technique is the same for both.

Also it is a very simple matter to successfully unite the ends of arteries and veins together. Since comparable arteries and veins are most convenient as regards proximity, operations thus far have been performed most frequently upon such vessels, as the common carotid artery and the external jugular vein; and as the vein is usually of the greater diameter, the same precautions are observed in making the union to avoid "puckering," as described for arteries of unequal size. By such operations the character and the direction of the circulation in veins and arteries may be changed almost at will. For example, if the central end of a common carotid artery be anastomosed to the peripheral end of an external jugular vein, the circulation in the latter becomes arterial in character, and the direction of flow is reversed. Or if the central end of a common carotid artery be connected with the central end of an external jugular vein, the character of flow in the latter becomes arterial. Likewise, if the femoral artery and vein be divided, and the ends crossed and united (central ends to peripheral ends), the venous channels peripheral to the line of operation carry arterial blood to the capillaries—*i.e.*, in the direction reverse of the normal—while

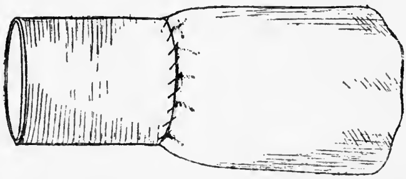

Fig. 48.—End-to-End Union of an Artery and Vein, showing Constriction of the End of the Vein to conform to the Artery.

the peripheral arterial channels return the blood back from the capillaries—that is, the arteries convey venous blood, and the direction of flow is the reverse of the normal (see p. 161).

But a vein may be with ease successfully united end-to-end with an artery much larger than itself. Thus the peripheral end of an inferior thyroid vein may be united with the central end of a common cartoid artery. Care is taken to uniformly take longer stitches in the edge of the artery in order to obtain a smooth, regular union. The results of all such operations, not only upon the vessels themselves (p. 83), but the results upon the tissues affected (p. 174) will be considered more fully in separate divisions.

Thus far only suturing of vascular injuries, including patching and end-to-end anastomoses, and interposition of tubular segments and suture of their ends to the ends of divided blood-vessels, have been considered. But other operations, consisting of anastomoses between the ends of vessels and lateral openings in the walls of vessels, for convenience termed "termino-lateral" or "end-to-side anastomosis," and anastomoses by lateral openings, termed "lateral" or "side-to-side anastomosis," are of interest and importance.

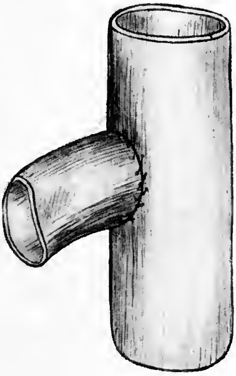

Fig. 49.—End-to-Side Anastomosis.

A termino-lateral or end-to-side anastomosis is performed by dividing a vessel, and preparing one end as described for an end-to-end anastomosis. The vessel into which the end is to be implanted is isolated, and a segment temporarily cut off from the circulation by suitable clamps. A circular opening, slightly larger than the lumen of the end of the vessel already prepared, is then made by removing a disc from the wall. This is done by firmly grasping the tissues of the wall at a point corresponding to the centre of the proposed opening, and removing the disc with keen scissors having curved blades. The blood is then pressed out of the segment, and removed with a sponge, as described for the preparation of a ragged injury in a vessel wall for suture (p. 65).

Next a fixing suture is passed from without inward through the edge of the wall, as in end-to-end suture, and a point on the edge of the wall of the end of the other vessel is pierced from within outward, and the ligature loosely tied and held while the second

fixing suture is placed. The first suture is the undermost one, considering the position in which the vessels will lie after the operation, and care is exercised to avoid distortion or unnecessary bending of the artery. The second suture is similarly placed one-third of the distance around the circumference of the lateral opening and of the margin of the end of the vessel. The two ligatures are then tied, and the last fixing suture placed and tied at the apex of the isosceles triangle, whose base is formed by the first and second stitches. Or four fixing sutures placed at equidistant points may be used. The cut edges of the vessels between the fixing ligatures are then continuously stitched together in the same way as in end-to-end anastomosis, and the operation completed by cutting off the ligatures, restoring the circulation, and closing the wound. This operation is especially indicated when an increased blood-supply for a part is desired, and at the same time it is undesirable to sacrifice the circulation through the vessel from which the supply is to be drawn, for example, in the arterialization and reversal of the circulation in the inferior thyroid vein by implanting its peripheral end into one of the common carotid arteries.

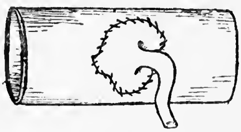

FIG. 50.—SHOWING END-TO-SIDE METHOD OF UNITING BLOOD-VESSELS, A PATCH SURROUNDING THE MOUTH OF THE SMALL VESSEL BEING REMOVED AND IMPLANTED.

If the branch thus added to a vascular trunk is of such small calibre as to render the operation too difficult or the result doubtful, a circular disc of suitable size, bearing the orifice of the vessel in its centre, may be removed, and set into a suitable opening made on the trunk of a vessel for its reception, the technique being a combination of that described for the repair of a vascular injury by inserting a patch and for end-to-end or termino-lateral anastomosis. This operation is valuable, especially in engrafting masses of tissues or organs whose blood-supply is carried through vessels too small to handle in the end-to-end fashion, as an ovary. But this will again be mentioned in the section on transplantations (p. 200).

Lateral or side-to-side anastomoses are the oldest abnormal, direct, anastomotic connections between vascular trunks observed, being occasionally produced by the rupture of an aneurism into a vein, or through acute or traumatic injury of blood-vessels, as in stab-wounds, or wounds made in lancing vessels for the purpose of bleeding. The essential mechanism appears to be simultaneous opening of an artery and vein, with passage of the arterial blood

into the vein. Thus some of the arterial blood is "short circuited" back to the heart—that is, it returns to the heart without traversing the capillaries. The very fact that such permanent communicating channels have been observed under such conditions speaks most strongly for successful blood-vessel anastomoses and the ease with which they may be performed. For under such circumstances the conditions must be favourable for coagulation, yet in some instances at least permanently patent anastomotic openings result.

When examined more closely, the most powerful factors probably concerned in leading to the result—that is, the factors preventing the laying down of an occluding thrombus—substantiate the views of the writer as to the factors to be considered as preventing this undesirable result in deliberately planned and executed vascular anastomoses—namely, the velocity of blood flowing over the foreign surface, or the ratio of unit mass of blood per unit area of foreign surface (per unit of time).

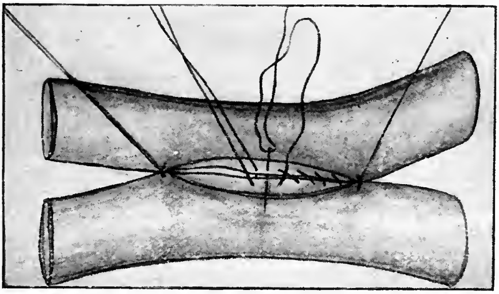

FIG. 51.—ECK'S FISTULA, SHOWING POSITION OF END-FIXING SUTURES, TEMPORARY MIDDLE FIXING SUTURE, AND METHOD OF SEWING FROM INTIMAL SURFACE.
Stitching should cross intimal surface transversely.

For in such cases the arterial blood flows through a short channel from an area of high arterial to an area of low venous pressure. So the speed, and therefore the volume of blood crossing the foreign surfaces, must be relatively great. And in further substantiation of this view is the conclusion, from results of operative anastomoses, that the more exactly these conditions are imitated, the more certain a permanently successful result. As instances, arterio-venous anastomoses—*e.g.*, central end of a common carotid artery to the peripheral end of an external jugular vein, or lateral anastomosis of the portal vein to the inferior vena cava (Eck's fistula), with ligation of the former where it enters the liver, may be mentioned.

The technique of making a side-to-side anastomosis consists largely in the application of the methods already described, to the morphological conditions of the operation. Both vessels are prepared, and openings made in them, as in the case of the vessel used

as a trunk in end-to-side anastomoses. The openings are made of approximately equal size, and of the same shape, so that when the margins of the surrounding walls are brought together they fit evenly. The openings in the vessels should be in width about one-third the diameter, and in length about one and one-half times the diameter of the vessel, if the entire circulation of one vessel is to be diverted through the anastomosis, as in Eck's fistula, with ligation of the portal vein. As in all similar anastomoses, the posterior fixing suture is placed first. But it is placed from the intimal surface, and is not tied, being later removed. Next, a similar suture is placed on either side at points distant one-fourth of the circumference of the openings. The end sutures are placed in a special way. Directing the needle from without inward, it is thrust through the margin of the wall of one vessel at a point on an imaginary line drawn longitudinally through the centre of the lateral opening. It is then pulled through, and, with the point directed from within outward, it is thrust through the wall of the other vessel at the corresponding point. This leaves both ends of the suture outside of the vessels in the **V** at one end of the **X** formed by the trunks of the vessels. The suture is then tied, which places the knot in the crotch formed by the vessels. Beginning at one of the sutures last placed, which may be termed " end sutures," and holding the edges of the approximated walls in favourable position for suturing by traction on the first-placed suture, which is termed the " posterior," the edges of the vessel are sewn together by the usual continuous suture, the chief difference being that the outer or adventitial surfaces of the vessel margins are together, and not the intimal, as has been the case in previously described operations. And the points of entrance and exit of the needle are on the intimal surfaces. When the posterior ligature is reached, one of its ends that has been used for traction is severed near the tissue, and the remainder withdrawn. The ends of the other end-fixing suture previously placed, but not yet employed, are then used for traction

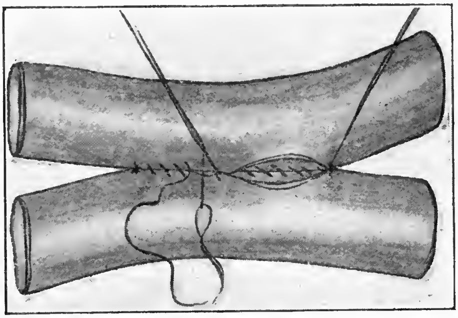

Fig. 52.—Eck's Fistula, showing Operation nearing Completion.

upon the edges of the wall to be sutured, between the point where it is placed and the posterior-fixing suture, and the laying of the continuous suture continued until the end-fixing suture is reached. The continuous suture is then tied with this suture, the knot being placed on the outer surface of the vascular wall. It should be noted that the continuous suture was not tied with the posterior suture. The reason for this is that it is unnecessary, and only serves to complicate and lengthen the operation. At this stage the edges sutured together appear rather rough, as they project inward and cause an abrupt longitudinal ridge on the lumenal aspect of the vessels. But the ridge formed by the edges of the vessels will largely or completely disappear owing to the pressing out of the walls and tension upon the line of suture—that is, by a kind of a leaf-hinge action, the edges will be moved outward, and the intimal margins approximated.

A fourth fixing suture is now placed in the anterior margins of the walls in the usual manner, passing the needle from without midway between the end ligatures, and tied. The continuous suturing is then continued from the end ligature where it was last tied to the fixing suture last placed, and tied with the loose ends. The remaining interval of free edges is then sutured, and the continuous suture tied with the end left at the original point of beginning. The ends of all ligatures are now clipped off within 1 or 2 millimetres of the vessels, the circulation restored, and the operation completed in the usual way. If much traction is likely to be exerted against the line of suture, it is well to place a staying suture in each crotch at either end of the suture line just distal to the primary end-fixing sutures, as these are the points of greatest strain. This is done by thrusting a needle, bearing a suture somewhat coarser than that used in suturing the edges of the vessels together, or the needle may carry an ordinary suture doubled, downward so as to take a firm stitch in the tissues of the wall of the vessel on one side of the crotch. The stitch need not penetrate the

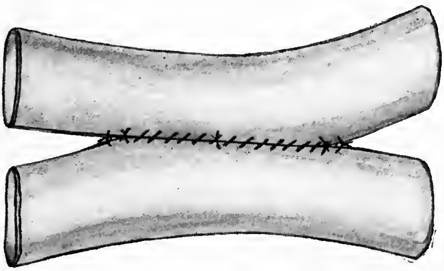

Fig. 53.—Eck's Fistula Operation Complete. For clearness of illustration the stay sutures at either end of the anastomosis are not drawn tight.

intimal surface, but this is somewhat difficult to gauge, and no harm will result if it does penetrate the intima for a short distance if the suture used is not too coarse. The needle is then drawn through, and directing the point upward a similar stitch is taken in the wall of the opposite vessel, and the ends of the suture firmly and securely tied, and cut off.

Lateral anastomoses may be made between a ligated and divided vessel and the trunk of another vessel, or between two ligated and divided vessels, the lateral opening in the ligated vessels being made near the end in order to avoid an excess of "blind end" after the operation is completed. By means of the ligatures on the vessels, the ends may be fixed to surrounding tissues in such a way that excessive traction upon the anastomosis will be prevented. By using an ordinary surgical needle, into which the ligature is threaded, the operation of anchoring the end of the vessel is facilitated,

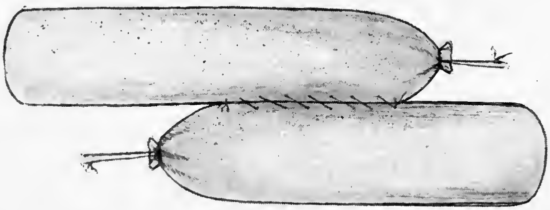

FIG. 54.—TERMINO-LATERAL ANASTOMOSIS OF BLOOD-VESSELS.
The ligatures on the ends of the vessels are of service in preventing undue retraction and strain upon the anastomosis, the ligatures being fixed to neighbouring tissues (see Fig. 58).

as no time is lost in firmly and securely attaching the ligature to a suitable point of the surrounding tissues by means of a stitch.

Another anastomotic operation, which is of particular interest in connection with tissue transplantations and will be considered in the division on that subject (p. 201), consists in removing a segment of a vessel bearing the mouths of one or more branching vessels, and engrafting the segment by anastomosing the ends with those of a divided blood-vessel in the manner already described.

These are the most important operations of this character hitherto practised upon blood-vessels, and it is left to the reader to judge of the merits or demerits of each from the evidence presented in these pages. But the opinion of the writer is that it is hardly fair to the various operations themselves to deal more severely with one than with another, for no doubt the apparent complexity of the technique would tend to at least prejudice the reader more

against some operations than others, while as a matter of experience some of the more complex appearing operations, as judged from the descriptions, are more successfully executed than certain of the more simple appearing ones. For example, an Eck's fistula is quickly and easily made. Even with methods much cruder in the sense that they leave more foreign surface exposed in the lumen of the operation than is the case with the method here described, the operation has been successfully performed many times in the last decade, and not infrequently by men of no considerable surgical experience. And the reason for this is clear when the occurrence of pathological or traumatic arterio-venous fistulas, in which class Eck's fistula in large measure belongs, although it is between veins, is considered (p. 77). Yet, as judged by the writer's description, the operation is among the more complex ones. So in forecasting a result many factors must be considered.

But all the operations described are perfectly successful as regards permanency of patency of lumenal openings and channels when properly executed and the conditions described fulfilled. So it may be concluded that not only are a large number of anastomotic operations on blood-vessels feasible, but the results as indicated by the circulatory function are satisfactory.

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CHAPTER IV

MORPHOLOGICAL RESULTS

It is evident that many different combinations of blood-vessels are possible, ranging from simple suture of the ends of a divided arterial or venous trunk to the engrafting of a segment of vein between the ends of a divided artery, with reversal of the direction of the circulation in the venous segment. But in this place only such combinations as have yielded results that contribute definite knowledge of the structural character of blood-vessels after such operations will be described.

The simplest class of operation—reunion of divided arteries or veins—appears to produce no structural alteration of note beyond the traumatic effects in the immediate vicinity of the line of suture.

Protocol.

May 7.—Dog 21 : young adult, black, male. Weight, 6·3 kilogrammes. Under ether anæsthesia both common carotid arteries were divided, and the central end of the left was anastomosed to the peripheral end of the right; twenty-five stitches and twelve minutes were required for the operation. The other end of the arteries were permanently ligated. The right external jugular vein was divided and reunited ; twenty stitches and ten minutes were required. The dog made an uneventful recovery.

May 17.—Circulation appeared to be good through both anastomoses.

May 27.—The animal was etherized ; after exposing the vessels, and demonstrating that the circulation was excellent, the specimens were removed (Fig. 57).

Protocol.

May 29.—Dog 6 : black bull-poodle, male. Under ether anæsthesia the trunks of both common carotid arteries were divided and the ends ligated. A lateral anastomosis near the central

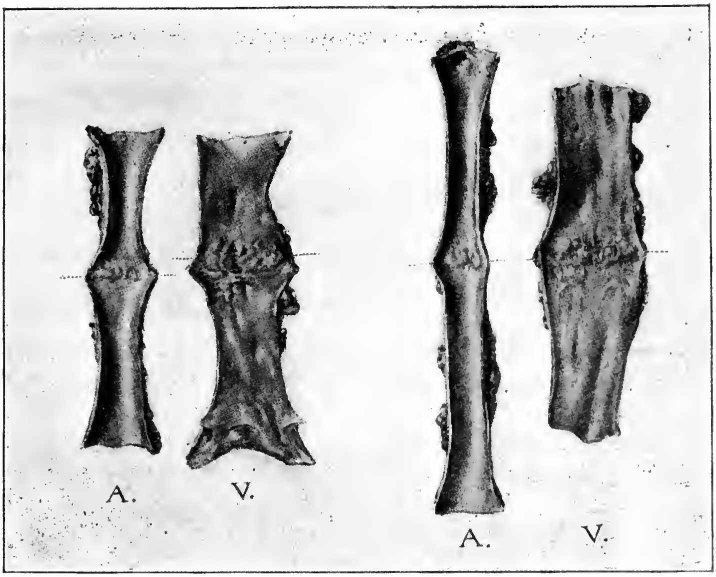


Fig. 55.—Circular Suture of Both Carotid Arteries and Both Jugular Veins, Forty-one Days after Operation. (Watts.)

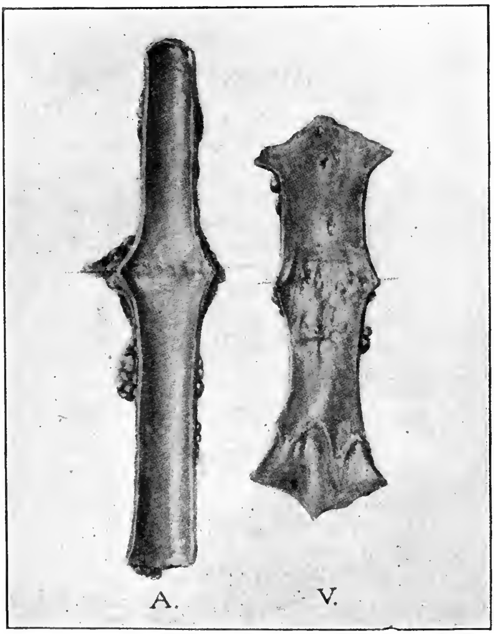


Fig. 56.—Circular Suture of Cartoid Artery and Jugular Vein, Forty-eight Days after Operation. (Watts.)

end of the left and near the peripheral end of the right, was instituted (Fig. 58).

December 19.—The animal was etherized; the circulation through the anastomosis was seen to be excellent. The specimen was removed. On longitudinal section the intima was smooth and glistening; the stitches were seen beneath it. The lumen was unobstructed.

The results of more complex combinations, the interposition of an arterial segment between the ends of a divided artery, and the interposition of a venous segment between the ends of a divided artery are illustrated by the figures, and are described below.

Protocol.

April 24.—Dog 18: old black-and-brown male cur. Weight, 9 kilogrammes. Purulent discharge from nose. Etherized.

Removed segments of the left external jugular vein, the right common carotid and left common carotid arteries. Inserted a segment of the left external jugular vein between the cut ends of the right common artery. Transplanted the segment of the right common carotid artery between the ends of the left common carotid artery.

April 28, *p.m.*—The dog was very weak, and there was much discharge from the nose. He would not eat or drink. The bowels were loose.

April 29, *a.m.*—Dog died.

At post-mortem examination the wound was dry and well healed. The deep neck sutures were in excellent condition. The right common carotid artery and the venous segment were in good condition, as were also the left common carotid artery and the segment of the right common carotid artery (Fig. 59). Opened thorax. Advanced purulent pericarditis, with pleural effusion, were present. A large quantity of purulent liquid was found in the pericardial and pleural cavities. The pericardium was enormously thickened.

Protocol.

April 29.—Dog 20: medium-sized adult dog. The common carotid arteries were exposed under ether anæsthesia. A small segment from the left was removed and preserved. A segment from the right was removed and interposed between the ends of the left. The right external jugular vein was exposed, and a segment removed

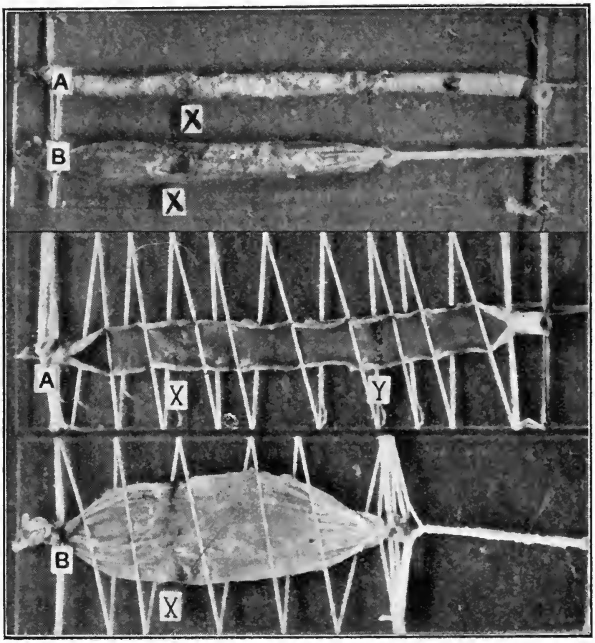


Fig. 57.—Anastomosis of—A, Carotid Artery to Carotid Artery; B, Jugular Vein to Jugular Vein, Twenty Days after Operation, External and Internal Surfaces.

X indicates line of anastomosis. Y indicates another line of anastomosis made the day before the animal was killed. (Dog 21.)

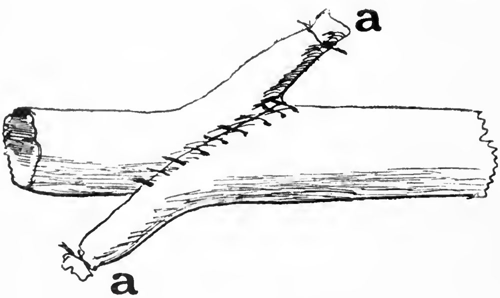


Fig. 58.—Termino-Lateral Anastomosis of Carotid Arteries.

Diagram of the union of the vessels seven months after the operation. a, a, ends of arteries ligated. (See also Fig. 54.)

and interposed between the ends of the right common carotid artery. The normal direction of the circulation in both segments was preserved. Very little sodium chloride (0·9 per cent.) solution and paraffin-oil were used. The circulation through both segments was excellent. The dog made an uneventful recovery.

May 12.—The circulation on both sides was excellent.

May 21.—The circulation on both sides was excellent.

May 27.—The carotid arteries were exposed, and a very active circulation through the segments was demonstrated. The specimens were removed (Fig. 60).

The arterial segment showed no marked changes except at the lines of anastomoses. With the venous segment the case was quite different, especially after some weeks, when it showed not only moderate and somewhat irregular thickening, but marked histological alteration.

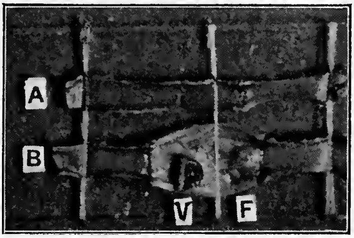


FIG. 59.—A, SEGMENT OF CAROTID ARTERY ON CAROTID ARTERY; B, SEGMENT OF JUGULAR VEIN ON CAROTID ARTERY, FIVE DAYS AFTER OPERATION.

V, indicates valve into the pocket of which a half-circular piece of black paper was inserted before photographing. F, indicates small lamellar white fibrinous deposit. (Dog 18.)

Macroscopically, the venous segment was of about the same size, or perhaps a little larger, than when last seen. Externally, it was fibrous and red, particularly in certain areas. Small circular ridges marked the points of anastomoses. On longitudinal section it collapsed. Two sets of valves, which appeared normal, were present, one set being near the distal end of the segment. In physical character the wall was pliable, but somewhat thickened, especially in the intervalvular regions. In the thicker areas it was opaque, while behind the valve-cusps it was quite transparent, and showed little if any thickening. The thickened areas were red, and were richly supplied with blood-vessels, while the thinner and more transparent areas showed slight or no evidence of such vessels. The intima was smooth and glistening throughout, and was continuous with that of the artery at either end. The stitches could be seen at the lines of anastomoses, but they were buried by a covering of newly-formed tissue in all respects similar to the surrounding intimal tissue. The surface presented a somewhat yellowish colouration. The mouths of a

number of small venous branches, which were ligated at the time of the operation, appeared.

Microscopically, besides an irregular thickening, the most striking features were evidences of œdema and retrogressive changes of a hyaline character ; complete absence of muscle fibres ; numerous newly-formed blood-vessels in the outer coats, most marked in the thicker areas ; masses of interstitial (extravascular)

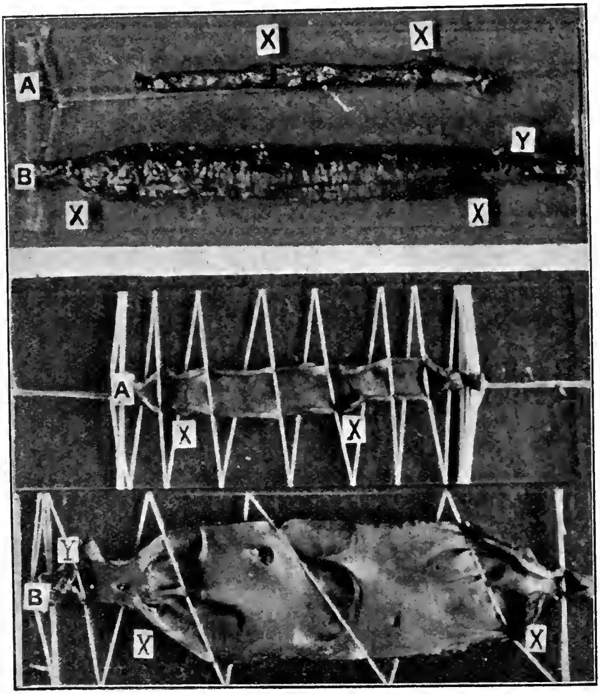


Fig. 60.—A, Segment of Carotid Artery on Carotid Artery ; B, Segment of External Jugular Vein on Carotid Artery, Twenty-eight Days after Operation.

External (adventitial) and internal surfaces of artery. X indicates line of anastomosis. (Dog 20.)

blood in the outer coats of the thicker areas ; and a very pronounced perivascular (periadventitial) fibrosis. At the lines of anastomoses the appearance was modified by the traumatic effects. The embedded ligature was separated from the lumen by what appeared to be the organized remains of a thin, band-like thrombus or fibrinous deposit, which presented a smooth surface, and was composed of flattened cells, with elongated nuclei (Baumgarten type of cells).

The superficial cells, though not identical in appearance with those of normal intimal endothelium, resembled them in general character and arrangement. Elastic fibres, which were fairly abundant, were chiefly of the coarser variety. For the most part they were longitudinally arranged, and occurred in the inner coats, and especially in what corresponded to the middle coat normally. The circularly disposed fibres were situated internally to the longitudinal ones.

Attention is called particularly to the fact that muscular hypertrophy was not observed, which is opposed to the observations of Watts, and to the more recent observations of Fischer and Schmieden, who reported an augmentation in muscular elements, both in size and numbers. But Watts did not especially study such changes, as he was investigating primarily the larger problem of the feasibility of vascular anastomoses. On the other hand, Fischer and Schmieden devoted special study to the matter. Also it should be noted that the writer's studies indicate that the muscular tissue of a segment of vein engrafted between the ends of a divided artery progressively decreases. This indicates that a certain time is required for the disappearance of such tissue failing to survive. And since the disappearance of a tissue after death is due to disintegrative and absorptive processes, and since the absorptive mechanism is no doubt thrown out of gear, owing to the interruption of the circulation in the capillaries of the vascular wall, such a result would be anticipated. This point very probably would do much in explaining the persistence of muscular tissue in engrafted vascular segments for considerable periods, and especially in tissues previously treated in such a way as to destroy or greatly lower their vitality as preservation in formaldehyde solution or cold storage. And to demonstrate the force of the argument, it is only necessary to observe the long time required for the disappearance through absorptive process of a thread of catgut introduced into the tissues.

Hetero-Transplantation.

A segment of rabbit's aorta interposed between the ends of a divided artery of a dog, though performing an adequate function as regards the transmission of blood, showed marked changes. A similar result was observed in an aortic segment from a cat similarly engrafted into a dog.*

* *American Journal of Physiology*, 1907, xxx. 482.

Protocol.

May 15.—Dog 2 : young adult, female, in fair condition. Weight about 11·3 kilogrammes. Large double goitre. A segment of the left common carotid artery, 0·5 centimetre long, was removed, and a segment of the abdominal aorta from a 3,000 grammes white, male rabbit was interposed, the segment being about 2·5 centimetres long. The arteries of the dog were considerably enlarged. The diameter of the common carotid artery was more than twice that of the engrafted aortic segment. The circulation was restored through the segment about one and a half hours after its removal from the rabbit.

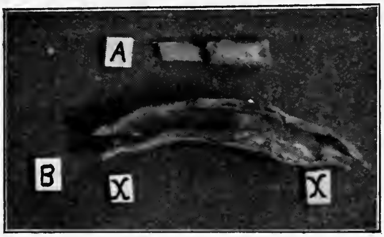


FIG. 61.—TRANSPLANTATION OF RABBIT'S AORTA ON DOG'S CAROTID ARTERY—A, AS AT TIME OF TRANSPLANTATION; B, SEVEN MONTHS LATER.

A portion of A was removed for histological examination.

June 15.—Under ether anæsthesia the wound was reopened, and the segment of aorta was found to have the same diameter as the carotid artery, and to be somewhat longer than at time of transplantation. The circulation was excellent.

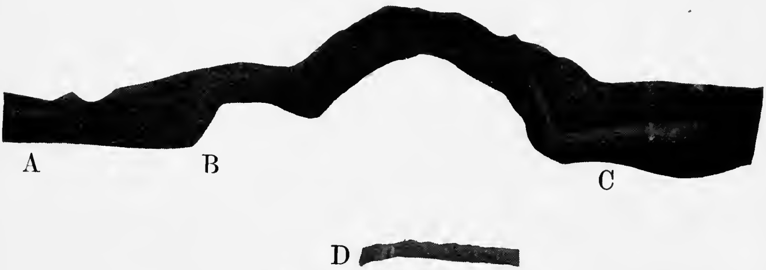


FIG. 62.—PHOTOGRAPH OF A MAGNIFIED LONGITUDINAL SECTION FROM ONE END OF THE SPECIMEN SHOWN IN FIG. 61.

A, end of dog's common carotid artery; B, beginning of rabbit's aortic segment; C, strongly calcified area. A fracture of tissues occurred at this point (very probably an artifact). Also there was a comparatively large space near the middle of the wall, apparently empty at this time. D is a longitudinal section of normal rabbit's aorta, mounted, sectioned, and stained with the engrafted specimen, and photographed under the same magnification.

December.—The transplanted segment was removed. The circulation at the time was excellent.

Macroscopically, the segment was much enlarged. It was greyish in colour, and densely fibrous in appearance. It was quite rigid, and on longitudinal section, which procedure indicated a considerable degree of calcification, the walls showed no tendency to collapse. Separation of the longitudinal edges was resisted by the rigidity of

Fig. 63.—Dog, between the Ends of whose Divided Common Carotid Artery (Right) a Segment of Formaldehyde Fixed Vena Cava of another Dog was engrafted.

The artery still pulsates, and the animal is in excellent condition more than three years after the operation.

the walls, and on forcing the artery open, rupture of the intimal surface occurred at the point of greatest extension. Except for this, the intimal surface was smooth and glistening, though presenting several cup-like irregularities, which were neither very abrupt nor deep. The intimal surfaces of the segment and of the artery at either end were continuous and smooth. The wall was

somewhat irregularly transparent. The lumen was much larger than that of the artery.

Microscopically, the wall varied in thickness from about three to six times its thickness at the time of transplantation. The intimal surface was smooth, and continuous with that of the artery. The tissues were stained irregularly and diffusely (hæmatoxylin - eosin). They were densely fibrous, and showed retrogressive changes of a hyaline character and areas of calcification.

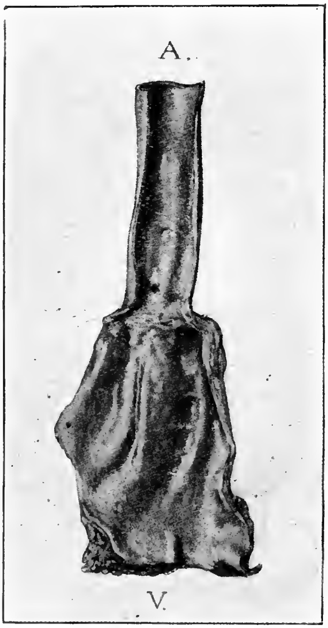


Fig. 64.—Circular Anastomosis of Femoral Artery and Vein, Three Months after Operation. Marked Thickening and Dilatation of Vein. (Watts.)

Fig. 65.—Circular Anastomosis of Carotid Artery and Jugular Vein, Three Months after Operation. Marked Sclerosis of Vein. (Watts.)

No muscle was present. The suture material was deeply buried at the lines of anastomoses. From near this point (line of anastomosis) the ends of the carotid artery appeared normal.

A segment of vena cava was taken from a dog, and preserved and fixed for sixty days in 2·5 per cent. formalin in 0·9 per cent. sodium chloride. It was treated with dilute ammonia, dehydrated in absolute alcohol, and impregnated with paraffin-oil, and then engrafted between the ends of a divided common carotid artery of

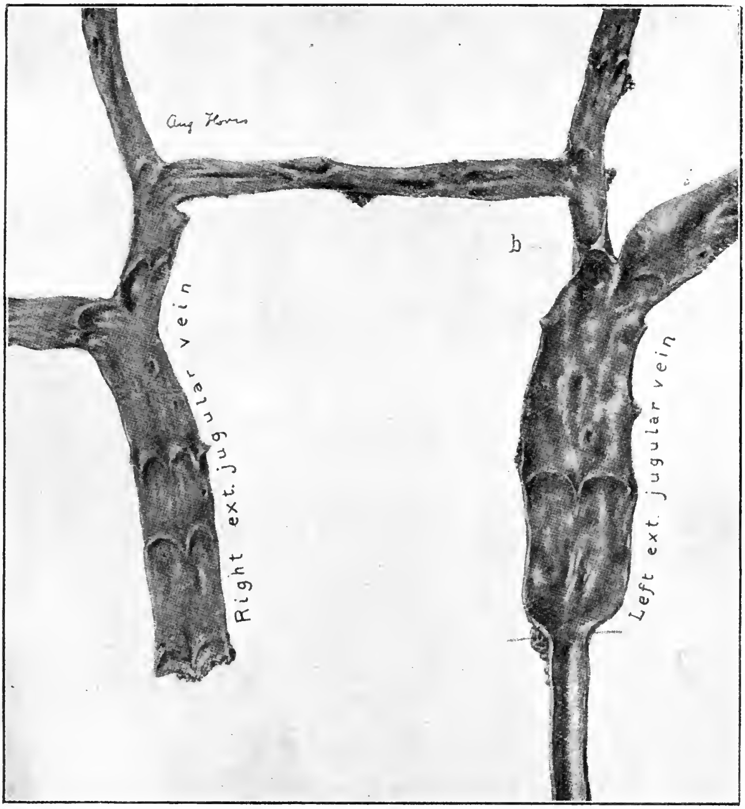


FIG. 66.—CIRCULAR ANASTOMOSIS OF THE LEFT COMMON CAROTID ARTERY AND LEFT EXTERNAL JUGULAR VEIN, FOUR MONTHS AFTER OPERATION. (WATTS.)

As a result of the arterial pressure, this vein is much thickened and dilated. Small branch of vein occluded (b) probably due to valves, being forced together and becoming adherent.

another dog. Excellent functional restoration was observed. Twenty-three days after the operation direct examination (under anæsthesia) revealed an excellent circulation, confirming the previous clinical examination, and the segment, though it showed some alteration, was performing its function well (p. 130). More

than three years have elapsed, and the carotid pulse is normal. Histological studies have not been made (Fig. 63). According to Levin and Larkin, who later reported similar experiments, considerable structural alteration should occur. But since their longest observation, uncomplicated by occluding thrombosis, was of but eleven days' duration, and was complicated by infection, the observation of ultimate structural results are still wanting. And their criticism of Carrel's views regarding the survival of tissues in hetero-transplantations, and of similar transplantations of tissues preserved in cold storage, though warranted from a theoretical standpoint, as I pointed out some years ago,* are not fully borne out by their experiments.†

Simple arterio-venous anastomosis, as in arterialization and reversal of the blood-stream in the distal end of a vein by uniting it with the central end of an artery, is followed by marked structural changes in the vein (*cf.* Figs. 64, 65 and 66).

Protocol.

June 15, 1907.—Dog 4: young adult, female. Good condition. Weight, 11·3 kilogrammes. Presents a large symmetrical and double goitre.

Under ether the circulation was reversed in the right inferior thyroid vein by dividing and anastomosing its peripheral end to the central end of the divided right common carotid artery. The subsequent circulation was excellent. The thyroid immediately became engorged, and showed strong pulsatory expansion and contraction, and commencing œdema. The wound healed rapidly, and the animal remained in good condition.

May 12, 1908.—The blood-vessel was re-exposed under ether and removed.

Macroscopically, the vein was somewhat larger in diameter, and the walls more rigid and thicker than normally. In colour it was pale and greyish. No marked vascularity was noted. Upon longitudinal section it did not collapse. The intima was smooth and glistening, and continuous with that of the artery. The actual line of blending of the arterial and venous tissues could only be detected by close examination. The wall appeared to be abnormally transparent.

Microscopically, the wall was thickened. The intima was smooth,

* *Journal of the American Medical Association*, 1908, l. 1035.
† *Cf.* Klotz, *Science*, 1911, N.S., xxxiii. 899.

and beneath it there was muscular tissue, though not an abundance of it. The remainder of the wall was dense, hyaline, and fibrous in character, and very few nutrient blood-vessels could be seen. The fibrosis was most marked external to the middle coat. In the latter was a moderate number of elastic fibres, chiefly of the longitudinal coarser type.

Experiment showing Results of Arterio-Venous Anastomosis after more than Five Years.

Dog O.—Made anastomoses between central end of the right common carotid and the peripheral end of the right external jugular vein, and the peripheral end of the right common carotid artery and the central end of the right external jugular vein.

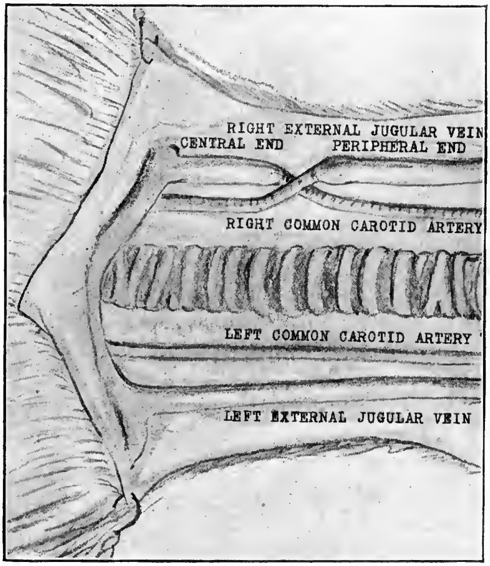


Fig. 67.—Showing Operation performed on Dog O. (See text.)

The animal made a prompt recovery. Pulse and thrill in peripheral end of the external jugular vein. That the pressure in the vein was less than arterial was indicated by the relatively slight pressure on the peripheral portion of the vein adequate to occlude the lumen, such pressure presumably being applied distal to anastomotic branches. By palpation it could be demonstrated readily that the pressure in the peripheral end of the external jugular vein was greater than in the unoperated vein. The animal remained in excellent condition, and gave birth to three litters of pups. More than five years after the operation the animal was killed in a fight with other dogs. At the last observation, sixteen days prior to death, the circulation was excellent. The day preceding death the animal was in good condition. At post-mortem examination the vessels were exposed by a medium incision down to the trachea.

Clotted blood was found in and between the subcutaneous and deeper tissues, but especially in the carotid sheath. The carotid artery on the operated side was found and traced to where it passed out through the neck muscles. It was strongly adherent to the muscular fascia at the point of exit. The point of anastomosis was at or near the point of adhesion. On opening the vessel longitudinally, the line of anastomosis was located by the lighter colour of the intima on the arterial side. By holding the specimen in a good light it was possible to make out about twelve slight longitudinal markings that in position correspond with the position of the stitches. The intima on the venous side was smooth, but the surface somewhat corrugated, due probably to the puckering of the vein necessary in order to reduce it to the size of the artery at the point of anastomosis. A few millimetres above the line of anastomosis a small pear- or heart-shaped mass was seen projecting slightly into the lumen of the vessel. It was continuous above with the wall, but the narrow portion directed downward was free. Passing the blade of a small pair of dissecting forceps upward beneath the free extremity, the point emerged through an opening near the centre of the attached portion. This channel no doubt transmitted blood during the life of the animal, and together with the free point projecting into the blood-stream was probably concerned in the production of the marked thrill which was so pronounced in the circulation in the peripheral end of the vein. The central end of the artery below the anastomosis was much more elastic than the peripheral end of the vein above the anastomosis. At the point of anastomosis a ridge was felt.

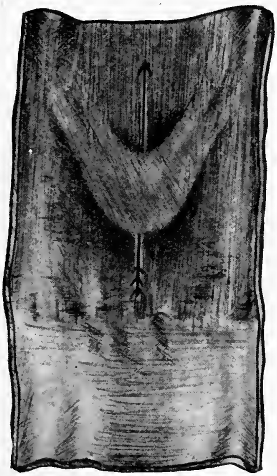


FIG. 68.—SHOWING LINE OF ANASTOMOSIS BETWEEN THE CENTRAL END OF THE RIGHT COMMON CAROTID ARTERY AND THE PERIPHERAL END OF THE RIGHT EXTERNAL JUGULAR VEIN AFTER FIVE YEARS (DOG O). ALSO SHOWS REMAINS OF VALVE IN VEIN.

The arrow indicates the opening through the valve flap, and also the direction of the blood-stream.

The line of anastomosis between the peripheral end of artery and central end of the vein was discovered by feeling a rather hard mass about the size of a pin's head. On opening the vessel longitudinally

this was found to be a localized thickening of the wall, due probably to puckering of the vein. The ligature was seen at this point beneath the intima, which was smooth and glistening.

The extensibility and elasticity of the vein below the anastomosis, tested by stretching with the fingers, was greater than that of the vein on the opposite side, but a little less than that of the artery above the anastomosis. The elasticity of the artery above the anastomosis

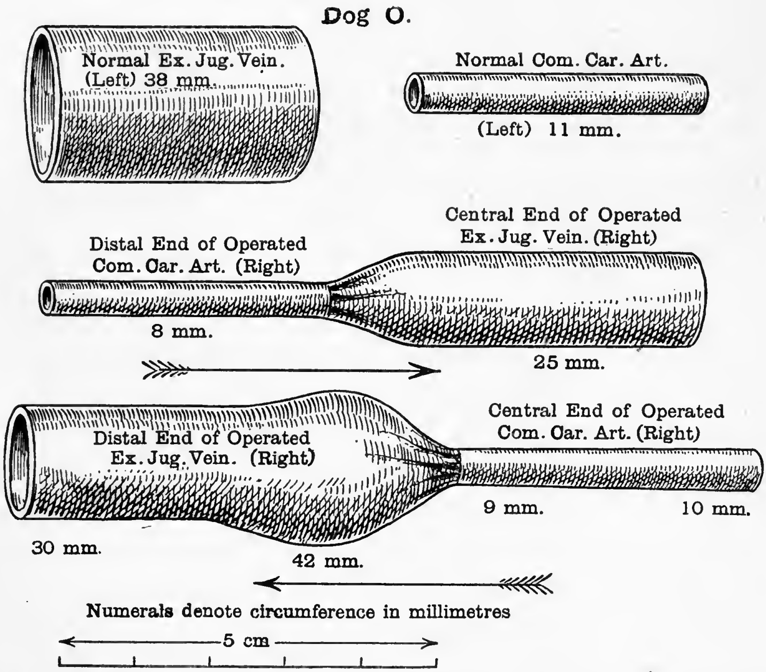


Fig. 69.—Showing Relative Sizes of Blood-Vessels following Arterio Venous Anastomoses more than Five Years after the Operation (Dog O).

Numerals indicate circumference of vessels; arrows indicate direction of circulation. Scale in centimetre divisions. (Diameters are drawn about 50 per cent. larger than scale.)

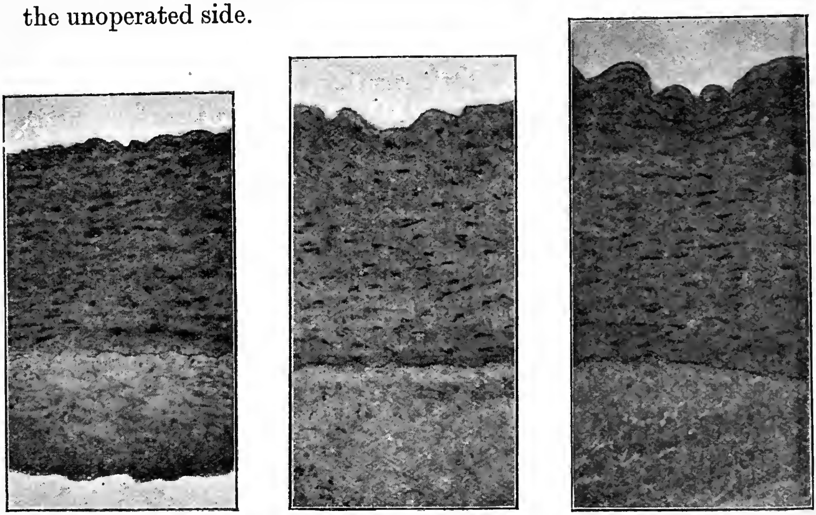
was about the same as that of the artery on the opposite side, but the resistance offered in stretching the artery above the anastomosis was less than the normal artery.

The superior thyroid branch of the normal artery was much larger than the same branch of the operated artery.

The thyroid lobe on the operated side measured 1·5 by 3·0 centimetres.

The thyroid lobe on the unoperated side measured 1·5 by 4·5 centimetres.

The lobe on the operated side was firmer in consistency than on the unoperated side.



UNOPERATED ARTERY. CENTRAL END OF OPERATED ARTERY. PERIPHERAL END OF OPERATED ARTERY.

FIG. 70.—RELATIVE THICKNESS OF COATS OF ARTERIES OF DOG O FIVE YEARS AFTER OPERATION.

Retouched microphotograph. Magnification the same in all. (See Protocol, and Fig. 69).

Measurements of the Walls of the Common Carotid Arteries and External Jugular Veins of Dog O.

	Intima and Media.	Adventitia.	Total Thickness.	Peri-adventitial.
	μ	μ	μ	μ
Normal artery	595·0	357·0	952·0	—
Central end artery	714·0	333·2	1047·2	9·0
Peripheral end artery ..	904·4	333·2	1237·6	—
Normal vein	119·0	238·0	357·0	—
Central end vein	249·9	292·5	542·4	14·0
Peripheral end vein	261·8	404·6	666·4	—

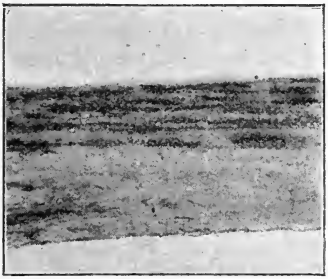
Histological examination gave the following results :

The wall of the unoperated artery appeared normal.

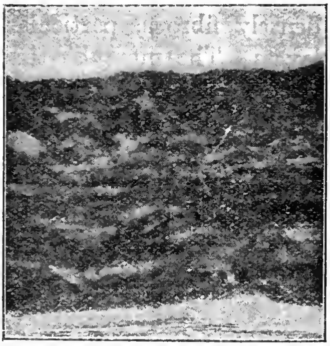
The wall of the central end of the operated artery was slightly thicker, and the lumen smaller, and the intimal surface more corru-

gated than the unoperated artery. The thickening was chiefly medial and periadventitial. The tissues otherwise appeared normal.

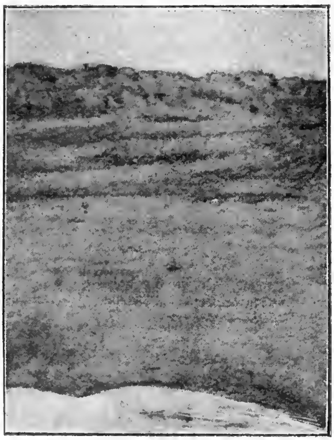
The wall of the peripheral end of the operated artery was thicker, and the lumen smaller, and the intimal surface more corrugated,



UNOPERATED VEIN.



CENTRAL END OF OPERATED VEIN.



PERIPHERAL END OF OPERATED VEIN.

FIG. 71.—RELATIVE THICKNESS OF COATS OF VEINS OF DOG O FIVE YEARS AFTER OPERATION.

(See Protocol and above figures.)

than in the central end. The thickening was chiefly medial; otherwise normal.

Quantitatively, the cross-sectional area of the muscular tissue of the media of the peripheral end of the operated artery was not increased, although the thickness of the medial was increased.

The wall of the unoperated vein appeared normal. The lumen may have been somewhat enlarged owing to the increased functional demands made upon it.

The wall of the central end of the operated vein was thicker and the lumen smaller than the unoperated vein. In structure it was densely fibrous, particularly the adventitial and periadventitial layers. The muscular tissue does not appear altogether normal, but complete studies have not been made.

The wall of the peripheral end of the operated vein is thickened, and the lumen, excepting for a short distance beyond the anastomosis, is smaller than the lumen of the unoperated vein. There is a fibrosis of all the coats, especially of the muscularis and adventitia.

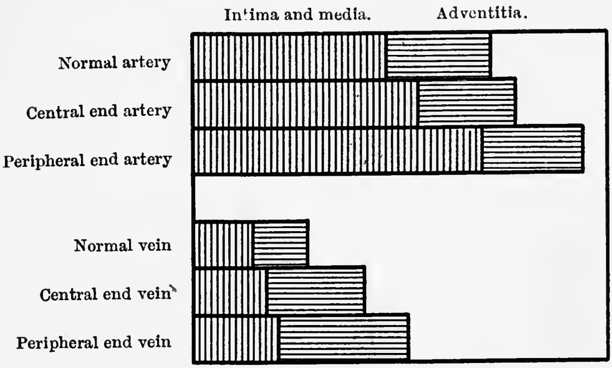


Fig. 72.—Showing Relative Alterations in Thickness of Vascular Coats after changing the Circulation, Five Years after Operation. (Dog O.)
Central end of artery connected to peripheral end of vein, and peripheral end of artery connected to central end of vein. The diagram was not constructed from the identical measurements given in the table on p. 98.

The muscle fibres are pale, and the layers are widely separated by fibrous tissue. The fibrous tissue has a less band-like arrangement, and is more homogeneous than in the central end of the vein.

Summary.

1. Union of arteries or veins, either end-to-end or by lateral openings, by through-and-through suturing as described, is not followed by structural alterations of note in the vessels themselves, excepting for the insignificant traumatic effects at the line of union.

2. In veins in which the circulation is changed to arterial and reversed, thickening is observed. Muscle tissue has been observed after five years. In the central end of a common carotid artery anastomosed to the peripheral end of an external

jugular vein, no very marked changes in the size compared to the unoperated companion vessel nor in the coats are observed after five years. In the central end of an external jugular vein anastomosed to the peripheral end of a common carotid artery more than five years, a decrease in the size and an increase in the thickness of the wall was noted; while the peripheral end of the artery is considerably decreased in size, and the wall is thicker, and the intima more corrugated, than in the unoperated companion vessel.

3. Eck's fistula in cats is not followed by vascular changes of note. Of additional interest is the observation that cats, during one and two years respectively, showed absolutely no clinical abnormalities even on an exclusively meat diet. This is at variance with the statement commonly made for dogs, the latter generally showing symptoms similar to ammonia intoxication (convulsions), said to be due to the incomplete conversion of the nitrogenous end-products of protein metabolism into urea, etc.

4. A segment of dog's carotid artery removed, and quickly engrafted between the cut ends of the other common carotid artery, after four weeks shows very little microscopic change, excepting for some thickening at the line of anastomosis.

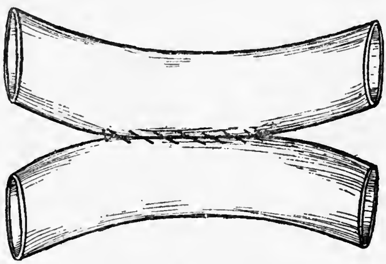


Fig. 73.—Diagram of Lateral Anastomosis (Eck's Fistula) between Two Blood-Vessels.

5. A segment of a dog's external jugular vein removed and quickly engrafted between the ends of a common carotid artery, the normal direction of blood-flow being preserved, after four weeks shows moderate thickening and indications of degeneration, particularly of the muscular tissue. A similar segment after five days shows much less change.

6. A segment of dog's external jugular vein removed and treated with salt solution, and engrafted between the ends of a common carotid artery, at the end of two weeks shows very much greater thickening than in the result above cited, but muscular tissue is present.

7. A segment of rabbit's aorta engrafted between the cut ends of a dog's common carotid artery, after seven months shows great enlargement, and enormous thickening and hardening (calcification) of the walls. Muscular tissue is absent.

8. A segment of dog's vena cava, preserved for sixty days in 2·5 per cent. formalin, then washed in dilute ammonia, dehydrated with absolute alcohol, impregnated with paraffin-oil, and then trans-

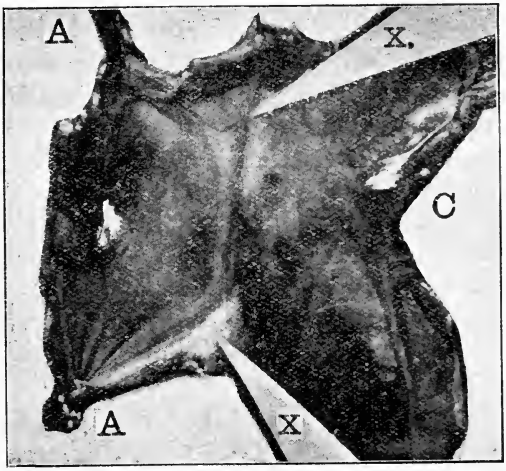


FIG. 74.—RESULT OF LATERAL ANASTOMOSIS BETWEEN THE PORTAL VEIN AND VENA CAVA (ECK'S FISTULA) OF A CAT AFTER MORE THAN A YEAR.

A, A, Ends of portal vein; C, vena cava. Specimen is laid open, showing smooth intimal surface. The line of anastomosis is indicated by the pointers, marked X, X.

planted between the ends of a common carotid artery of a bitch, three weeks ofter the operation shows an active circulation, but marked enlargement. After more than three years the pulse in the artery is still good.

Discussion of Structural Alterations observed in Blood-Vessels after Vascular Operations.

It might be anticipated that such experiments would cast some light on the nature of the processes resulting in the pathological conditions of similar anatomical character observed in blood-vessels—*e.g.*, arterio-sclerosis. Indeed, a considerable number of statements from this view-point have already appeared in the literature. I may here be permitted to recall attention to the early statements of Carrel and myself on this phase of the subject, and to my later statement calling attention to the complexity of the factors concerned in such observations. But I shall now show that notwithstanding the soundness of the theoretical considerations,

the information gathered up to date unfortunately does not distinctly advance our knowledge of such pathological processes.

The anatomical changes observed in transplanted blood-vessels having been described, it will suffice to say that they vary extremely. For example, rapidly-made autografts may show but slight structural changes, while heterografts similarly made may show great changes—so great, in fact, that the normal morphological and histological characters may largely disappear. Autografts made with tissues exposed to the prolonged action of harmful agents, such as salt or formaldehyde solutions, show similar alterations, the degree of such change apparently bearing a close relation to the degree of harmful influence to which the tissues have been exposed.

Other factors, such as character of the blood and direction of the blood-stream, alterations in the blood-pressure, and discontinuity of lymphatic and nervous connections, though perhaps not without influence, probably are of a lesser magnitude of importance in determining such structural changes. This applies particularly to the character of the blood, the direction of the blood-stream, and the discontinuity of lymphatic connections. Lastly, the interruption of the nutrient blood-channels, the vasa vasorum, very probably introduces a factor of appreciable magnitude. These factors will be taken up *seriatim*, and discussed more or less in detail.

Physiological Considerations.—The explanations of the structural changes observed in engrafted and in anastomosed blood-vessels are essentially physiological. It is seen in certain cases that certain tissues—*e.g.*, inner intimal cells—may present more or less normal characters, while others—*e.g.*, muscle—wholly disappear. Between these extremes one finds various degrees of normality of the tissues. There is an increase in certain tissues—*e.g.*, fibrous. Now, these differences are due, no doubt in part, to differences in situation. For example, it is said by pathologists that the endothelial cells of the intima are able to carry out their metabolic processes adequately directly with the blood in the lumen of the blood-vessel, which may be termed " functional blood " in contradistinction to nutritional blood in the capillaries of the vasa vasorum. The exact depth to which such an adequate metabolic commerce between the functional blood and the tissues may penetrate the vessel wall is not known, but perhaps not beyond the deeper tissues of the intima ; for, according to Mott, degeneration of the media is often

primarily due to obliteration or obstruction of the vasa vasorum, and consequent defective nutrition of the muscular fibres. Similarly the outermost layer of the wall of the vessel would be in a better position to carry on metabolic processes with the blood in the vessels of adjacent tissues than the deeper middle layer. Since it has been known for a long time that the circumferential elements of tissue masses engrafted by the simple method present evidences of better survival than those more centrally situated, the more marked retrogressive changes in the middle coat of such transplanted vascular segments is not surprising.

Also a possible difference in resistance to the abnormal conditions must be considered. It is well known that *different tissues exhibit different resistances to anæmia,* not only as evidenced by tenacity of preservation of function, but by ability of recuperation of function under resuscitatory measures, and by preservation of anatomical structure. Illustrative of these properties is the picture presented by an animal (cat), in which the arterial circulation to the head is suddenly decreased or entirely shut off (see p. 315). The most highly-developed centres (cerebral) appear to succumb first, as shown by loss of consciousness (also seen in fainting), then eye reflexes, respiratory centre, etc., in the order given, the entire process occupying but a minute or two. The same picture is seen in a head after rapid amputation, as in a fowl's head struck off with an axe. The train of clinical expressions of the passing of the nervous tissues into a state of oblivion (inactivity) is surprisingly constant.

If, after all the clinical evidences of nervous activity have disappeared, the circulation be restored (in the case of anæmia by arterial compression by release of the arteries, or in the case of amputation of the head, by restoring an arterial circulation by perfusion, or by engrafting on to another animal), return of function, as indicated by clinical manifestations (reflex and voluntary movements) may be witnessed. In general, recovery may be said to take place in inverse order to the susceptibility of the tissues to anæmia (asphyxia). If the period of inactivity be not too long, evidences of complete recovery of even all of the highest nervous activities may be seen. If, however, the period of anæmia be prolonged beyond a certain time, only the so-called lower centres—*e.g.*, respiratory—may appear to completely recover, the higher ones showing only partial recovery, or evidences of their recovery may be entirely wanting. Indeed, a condition in cats resembling insanity has been

observed following resuscitation of the brain after a prolonged period of anæmia.

The changes wrought in the cells of the tissues of the central nervous system by asphyxia also point to the conclusion that a relative susceptibility to an adverse condition in the elements of the nervous tissues exists. That such changes occur has long been known, but recently Pike and Gomez (p. 325) have studied the tissues of brains and spinal marrows which had been subjected to varying periods of anæmia, the results of which point most clearly to the conclusion above stated. It may here be remarked that drugs, various abnormal states, and even functional states as fatigue, produce similar cytological changes. And, further, since all these conditions affect the respiration of the tissues, the known tendency in many cases being toward asphyxia, to me these facts are evidences of the correctness of the view that many drugs produce certain clinical symptoms in virtue of properties of interfering with respiratory processes, and that the same is probably true in many pathological and abnormal conditions, not ordinarily attributed to asphyxia.

From this standpoint it would seem that to attribute the primary clinical changes to such cytological alterations (chromatolysis, etc.) is illogical. To illustrate : If an animal's head be struck off, and a bit of tissue from the brain be removed after ten minutes or so, and fixed and examined cytologically, relatively slight evidences of chromatolysis, etc., will be seen as compared to a similar tissue taken from a similar animal after resuscitation from apparent death from a period of cerebral anæmia (asphyxia) of the same length. Now, abnormal clinical symptoms after resuscitation cannot properly be attributed to the cell changes, asphyxia being the primary cause. Indeed, after such treatment such a cell may perhaps remain in a state of asphyxia for a long time, due to an inability to carry out a normal respiration owing to the injury wrought by the primary asphyxiation. Thus the view that much light can probably be thrown on the clinical phenomena following the administration of drugs (poisons), as well as those observed in numerous abnormal and pathological conditions from the standpoint of tissue respiration, seems worthy of further pursuit.

Similarly, *different* tissues show differences in susceptibility to anæmia (asphyxia) and in powers of recuperation. In general, it may be said that the more highly organized and developed a tissue the more delicate it is in this respect. Any such general statement,

however, only roughly approximates the order in which the tissues stand in susceptibility to asphyxia.

More specifically, the more abundant tissues found in segments of arteries and veins probably stand in about the order of nervous, muscular, fibrous, and endothelial as regards susceptibility to anæmia (asphyxia, autolysis, etc.). The basis of the statement for nervous tissue is the common statement that nerves degenerate when cut off from their "trophic centres," and only reappear by an ingrowth from the central tissues. A good illustration of the resistance of the intimal endothelial cells is the discovery of Professor Wells that, subjected to autolytic conditions, the endothelial cells of the intima exhibit the strongest resistance.

Finally, *the regenerative powers of the tissues* have to be taken into account, as a very considerable difference in this respect is known to exist. For example, it is commonly held that in mammals the cells of the central nervous system, and muscle fibres as well, are incapable of regeneration, while epidermal and fibrous tissues exhibit a very marked ability in this respect. Also, fibrous tissue is prone to replace other tissue that has suffered destruction, either by trauma or through retrogressive processes due to numerous agencies. As illustrative of the remarkable proliferative powers of the intimal cells, and of very striking interest in connection with complete biterminal vascular transplantations, is an observation by Professor Adami. He observed a complete intimal lining in an aortic dissecting aneurism which extended from the thoracic to the iliac region, the case presenting a history indicating that the aneurism was of not more than a few weeks' standing.

It is interesting to consider the results observed after simple injury of the intima, as well as intimal interruptions such as occur in vascular anastomoses (p. 58). It will be recalled that these findings show that at a time when the reparative processes have resulted in the gross appearance of intimal repair (lamellar white thrombi), microscopical examination shows that the newly-laid-down materials are not identical in appearance with normal intimal endothelium. Indeed, it is shown by the occurrence of non-occluding thrombi that abnormal surfaces may simulate an intimal surface in being smooth and glistening, and in being at least inert in so far as inducing fibrin deposition from living blood in contact with its surface is concerned. An observation by Guthrie in 1830 is interesting. The left subclavian artery was closed at its origin by a coagulum, leaving a channel through the centre for the blood-

stream. The canal in the coagula seemed smooth, as if lined by a false membrane. The question naturally follows, May the tissues of non-intimal origin assume the general character, and functionate adequately in place of a normal intimal surface? Or is such restitution of intimal continuity achieved by the ingrowth of neighbouring intima, or by the outgrowth or penetration of intimal tissues through the fibrinous deposit from the bottom of the wound? Although, as I am fully aware, the latter two views are the more orthodox, I am as yet unconvinced of the impossibility of tissues of other than intimal origin assuming such a function by an adaptive differentiation. According to Hektoen, a thrombus is regarded as an absolutely dead mass, and in reorganization replacement fibrosis takes place from the vessel wall.

The character of the blood circulating in an engrafted segment or anastomosed blood-vessel may have an influence in determining the resulting structural changes. For example, a vein may be caused to carry arterial, and an artery venous, blood (p. 157). Since, as before stated, the tissues near the intimal surface are said to take nourishment from the blood in the lumen of the vessel, such alteration of the blood may be an appreciable factor in the results; normally the metabolism of such tissues in veins may be considered as attuned to venous blood, and such tissues in arteries attuned to arterial blood. In the former case, arterial blood would at first sight appear to favour greater activities on the part of such tissues, but this cannot be considered as established until more data are obtained. The mere carrying of more blood to a part, or the better arterialization of blood, is not necessarily followed by increased activity on the part of the affected tissues. Indeed, there is evidence that the opposite condition, a condition similar to a state usually considered as peculiar to the pulmonary respiratory mechanism, termed "apnœa," which is observed best after a hyperoxygenation of the blood, together with a decreased content of carbon dioxide, as after a period of rapid pulmonary ventilation, may result. On the whole, the theoretical evidence is much stronger that tissue normally supplied abundantly with arterial blood—*e.g.*, an artery—would probably be more affected by causing the blood-supply to become venous. The results of the arterialization of the circulation in a vein are given on p. 95 (Dog O).

Direction of the blood-stream is a possible factor in the results. But excepting for the valves in veins, no strong argument either for or against the view can, so far as I am aware, be decisively supported at the present time.

Alteration of blood-pressure is a factor of great interest, not only in the interpretation of structural alterations in operated vessels, but also when considered in connection with sclerosis and related conditions often found in blood-vessels. In the case of a segment of a large vein engrafted between the ends of a divided artery, the pressure in the segment is greatly and continuously increased. For the maximum pressure in a vein, such as the external jugular, as a rule is not more than the equivalent of a few millimetres of mercury, while the pressure in such a vein engrafted upon a large artery, such as a common carotid, is increased perhaps more than twenty-fold.

The resulting structural changes observed in such a segment have already been described, so it will be enough to say that, compared to a similar venous segment engrafted between the ends of a divided vein, the changes appear to be much more pronounced, though it must be stated that a sufficient number of exact observations on the latter operation are as yet wanting. But enough is known to warrant the conclusion that structural alterations suffered by a venous segment on an artery are the more marked.

An analysis of the physical factors resulting from such an increase in pressure in the lumen of the vein is interesting. First, the tissues of the wall are subjected to an abnormal strain, but since of comparable veins and arteries the veins are said to be capable of withstanding as great or greater hydrostatic pressure than arteries, no fears need be entertained as to the adequacy of the veins in withstanding the arterial pressure without danger of rupture. The relatively great pressure subjects the tissues to an abnormal strain, and, although physically adequate, the ultimate effect of such strain on the tissues is problematical. Professor Adami regards the thickening of the wall of such a venous segment as due to strain hypertrophy. But if I understand his interpretation rightly, in the light of the results stated earlier I cannot accept this view. For the hypertrophy meant is in the nature of an active process, the physiological (non-inflammatory) response of the tissues to an increased functional demand, resulting in an abnormal development of the tissue elements. As he puts it, "moderate increase in the work which a tissue is called upon to perform is followed by overgrowth of that tissue, whereas excessive work is followed by rapid exhaustion and atrophy."

Now the question arises, Can the increased work thrown upon the transplanted venous segment (ignoring the pernicious influences

introduced by the operative procedures, as well as the resulting unfavourable, nutritional conditions) be considered as moderate? Also, do the resulting structural changes conform to the picture drawn of a work hypertrophy? To me it seems that only a negative answer can be given. Take, for instance, the structural changes. My observations lead to the conclusion that the muscularis wholly disappears within a few weeks, and the thickening is greatest, not in the intima, as might be anticipated from the more favourable nutritional situation, but in the outer coat. The conditions and the findings agree more nearly with Adami's description of the picture of overwork, a passive rather than an active condition. To "rapid exhaustion and atrophy" I would add "and perivascular fibrosis" to make the description of the picture seen in such a venous segment complete.

The overstrain placed upon the tissues, as well as the compression by the increased pressure in the lumen, would seem not only to be directly unfavourable to the carrying out of metabolic activities, but, by tending to compress the lymphatic spaces and the capillaries of the vasa vasorum, also to act indirectly.

Various drugs have been employed for the purpose of increasing the arterial blood-pressure in order to observe the effect of increased pressure upon the vascular walls. But such results are inconclusive, owing to the possible and even probable action of drugs directly upon the tissue elements (*cf.* Klotz).

Professor Klotz has offered strong experimental evidence that mechanical increasing of the pressure in arteries within moderate limits, without operative procedures on the vessels themselves, may lead to vascular hypertrophy in rabbits. The earliest and most marked hypertrophy was found to occur in the musculo-elastic layer of the intima.

As regards the lymphatics and vasa vasorum but little is known. As to the latter, in an engrafted vascular segment, since the connections are severed, the result of compression of the capillaries is problematical. In the case of the lymphatics, still less may be said. When the circulation is caused to become arterial and reversed in a vein, the conditions are perhaps vastly different, particularly as regards the vasa vasorum. I presume that the venous vasa vasorum open into the veins, but just where for any given vein I am unable to discover. But supposing that when the circulation is reversed in an external or internal jugular vein that the venous vasa vasorum for the peripheral portion of the vein opens peripherally to the line

of anastomosis (a point on which I am by no means certain), then the condition in the nutritional vessels of the vein (vasa vasorum) would theoretically approximate hyperæmia of the vein, as when an inferior thyroid vein is ligated, divided, and the peripheral end anastomosed to the central end of the opposite common carotid artery (*cf.* p. 166). And the histological findings in such a vein in certain respects bear a striking similarity to the findings in the case of the thyroid gland after such an operation as the one described—namely, a fibrosis consisting of densely packed fibres. Since theoretical explanations are elsewhere offered in explanation of the changes observed in the tissues of thyroid lobes thus operated upon (p. 187), and since the same considerations probably hold, with but slight modifications, for veins, it will suffice to say that the condition probably results in the production of partial asphyxiation under the influence of which the processes resulting in the structural changes described occur, the processes thus set up apparently being self-limiting.

Severance of nervous connections is a factor possibly contributing to the results, for it is well known that certain tissues undergo structural modifications after section of the nerves going to a part. This seems attributable not only to the loss of impulses through which certain functional mechanisms are thrown into activity or are governed, but also to the causing of nutritional disturbances, largely, perhaps, through alterations in the circulation.

Several authors claim to have obtained positive arterial lesions of a character of arterio-sclerosis by irritating or severing the nerves of the legs, but in each case the influence of the trophic inflammatory disturbances extending from ulcers about the limbs cannot be excluded (Klotz).

To be brief, I may say that no direct evidence has been obtained that nervous connections with an engrafted segment are formed. But special methods of investigating this subject have not been employed. It is, I think, reasonable to suppose that nerves very probably penetrate such tissues along with new blood-vessels, and as the latter may occur in abundance, from this standpoint it may be said that at least certain kinds of nerve fibres very probably grow into such engrafted vascular segments.

Under optimum conditions, as when an arterial segment is removed and immediately replaced, it would seem probable that a very complete re-establishment of nervous connections may occur. But in those cases where great degenerative and structural altera-

tions occur, it is highly doubtful if very extensive nervous connections are formed, as in heterografts or grafts made with dead tissues. In these cases major contractile tissues—*e.g.*, the muscularis—may be entirely absent, so, even though a very complete nervous mechanism develop, which is improbable, certain kinds of fibres would no doubt disappear through degenerative (functional atrophic) processes.

Other factors, such as the toxicity of the host's blood for the graft, as in hetero-transplantations, receive attention in the following chapter.

From the considerations above set forth, I am of the opinion that, basically, the structural alterations noted in engrafted vascular tissues are the expression of the sum total of a considerable number of factors, all of which primarily act through affecting the nutrition of the tissue. Also, that the changes observed so far are, on the whole, of passive, rather than of active, origin, and there is no evidence in any instance that a true functional hypertrophy may occur in such engrafted vascular segments.

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PART II

CHAPTER V

APPLICATIONS OF BLOOD-VESSEL SURGERY

As a result of the development of a simple and efficient method of vascular anastomoses, a wide biological field is opened to experimental investigation. But it will suffice here to give it but a rapid survey.

Morphological and microscopical study of the vascular tissues themselves has yielded information as to the power of the tissues to resist harmful influences to which they are exposed in the course of the operative procedures—namely, exposure to room temperature; mechanical manipulation; complete shutting off of the circulation in the vessel, both in the lumen and in the nutritional vessels (vasa vasorum); shutting off lymph-channels; total excision resulting in complete severance of all nervous connections; and upon the adaptive power of such tissues under altered circulatory conditions.

Notwithstanding the multiplicity of abnormal conditions under optimum circumstances, an engrafted vascular segment may not only retain its mechanical circulatory function, but its anatomical structure as well to a very high degree. It may even be called upon to perform an abnormal function, as when a segment of vein is inserted into an arterial trunk, and yet change in anatomical structure may be surprisingly moderate. As yet, these statements may only be applied to autografts, but there is some reason to hope from results obtained with other tissues that, at least in closely related individuals of the same breed, similarly perfect morphological results with isografts may be obtained.

In the case of heterografts it is known that the anatomical results are quite different. In fact, there may be no evidence that any of the original tissues survive, and structurally such a vascular segment may ultimately present great abnormalities—*e.g.*, fibrous thickening and calcification, together with enormous enlargement.

Yet the mechanical circulatory function may remain quite efficient. In interpreting such results, it would seem that with our present knowledge a consideration of the biolysins (or biotoxins) would be rational. From the same standpoint it is conceivable that perhaps by preliminary processes of immunization of the donor or recipient, or both, different results might be observed.

Since under certain conditions autografts may retain in a relatively high degree their normal anatomical structure, and since similar segments exposed to the action of solutions of drugs may show well-marked structural alterations, it would seem to be a promising method of comparing the toxicity of such substances and other agents.

The results attending the engrafting of preserved vascular tissues —*e.g.*, formaldehyde fixed, or tissues that have been subjected to a prolonged action of protoplasmic poisons, and which, therefore, certainly have no spark of latent vitality—are particularly of interest as regards the information yielded on the circulation of the blood, especially that an arterial blood-stream may be adequately transmitted by a dead (foreign) structure with no undesirable coagulation; the apparent replacement of the dead tissue by tissues presenting vital qualities; and the adequate vitalization of the dead tissue, with no indication that the mechanical circulatory function of the vessel is jeopardized. It may be remarked that phenomena of a similar order seem to occur in heterografted vascular segments.

In simple repair of the blood-vessels *in situ,* as when a mere opening in the wall of either an artery or vein is repaired, healing rapidly occurs; and if stenosis is not great, the histological structure of the tissues of the wall surrounding the injury apparently is not altered, barring the traumatic effects. Reunion of the ends of the divided vessels apparently results in no marked change in histological structure, excepting in the immediate vicinity of the line of union. The same seems true also when the central end of a divided vessel is united to the peripheral end of another divided vessel of similar kind and size, and the result uncomplicated by stenosis. The results of partial or complete stenosis of blood-vessels are dealt with in another place (p. 142).

If the central end of a divided artery be united to the peripheral end of a divided vein—*e.g.*, the central end of an external or internal jugular vein, or to an inferior thyroid vein—a rather well-marked, but by no means extraordinary, thickening of the wall of the vein ensues, while the arterial wall *appears* to decrease

slightly in thickness if the anastomosis and venous channels—*e.g.*, external jugular vein—permit the blood freely to escape, but sufficiently exact observations on this point are wanting; while such anastomosis to a smaller vein of a terminal character is followed by a thickening of the arterial wall with internal fibrosis and a narrowing of the arterial lumen not unlike the processes observed in simple arterial stenosis.

A fuller discussion of the vascular changes, particularly factors concerned in their production, is given under the physiological considerations (p. 103).

Observations on tissues engrafted with anastomosis of their blood-vessels are of very great biological interest. As an instance, the experiment designed for temporary results or organ perfusion may be cited.

In studying the functions of organs, a method fruitfully employed by physiologists consists in isolating the organ (*in situ*, or it may be completely removed from the body), and perfusing it through its blood-vessels with blood, or with some one of the so-called artificial blood or physiological solutions—*e.g.*, isotonic sodium chloride, Ringer's or Locke's solutions—with the view of preserving the activity of its normal functions. But owing to the rapid deterioration of tissues under such treatment, results obtained from the experiments, though yielding much valuable information, have not been altogether satisfying.*

In general it may be stated that the greatest technical difficulties have been experienced not only in procuring an adequate perfusion liquid and in its oxygenation and purification (removal of respiratory and urinary products—*i.e.*, end-products of tissue metabolism)

* Howell and Greene's Solutions.

		Per Cent.	Gm. per Litre.
I.	NaCl	0·700	7·00
	$CaCl_2$	0·026	0·26
	KCl	0·030	0·30
II.	NaCl	0·700	7·00
	$CaCl_2$	0·066	0·66
	KCl	0·040	0·40

Locke's Solutions.

		Per Cent.	Gm. per Litre.
I.	NaCl	0·900	9·000
	Dextrose	0·100	1·000
	$CaCl_2$	0·020	0·200
	KCl	0·020	0·200

II. The same solution, with the addition of 0·1 gramme of sodium bicarbonate per litre.

—but in the fulfilment of the physical conditions of the circulating medium, as suitable pressure and constant temperature of the solution.

Blood is, of course, readily obtainable, but as it is necessary to render it incoagulable either by injection or addition of anti-coagulant substances—*e.g.*, leech extract—or by defibrinating, its normal characters are not preserved. Indeed, it is said that so seemingly slight an alteration as the intermittent withdrawal, defibrination, and reintroduction of blood into the vessels of the animal from which it was withdrawn is sufficient to cause impairment of renal activity, even though the circulation remain good.

As to the artificial solutions used as substitutes for blood, as is well known even under optimum conditions, they are entirely unsatisfactory for many such purposes—*e.g.*, it is impossible to long maintain evidences of cerebral activity by perfusing the isolated mammalian brain with such a solution, the results being controlled by preservation of evidences of cerebral activity for a time in similar brains, with the same apparatus and technique, by using the animal's defibrinated blood.

This subject is of such interest that a partial abstract of a short paper by Drs. Stewart, Pike, and the writer, is given.*

Laborde is said to have perfused the isolated human brain, using the heads of decapitated criminals and the blood of dogs and oxen. In one case he connected by glass tubes the left carotid artery of the head with the corresponding carotid artery of a vigorous dog, and into the right carotid artery of the head he injected defibrinated ox blood. The perfusion was begun about eighteen minutes after decapitation. Stimulation of the Rolandic area of the cerebral cortex, which meanwhile had been laid bare, caused movements of the orbicularis palpebrarum muscle, of the eyebrows, the supra-orbital portion of the frontal muscles, and the elevators of the jaw—phenomena which persisted fifty minutes. In no case did Laborde get any return of voluntary movements.

Hayem and Barrier decapitated dogs and perfused the heads with defibrinated blood in five experiments, and entire blood in seventeen experiments, using bottles filled with blood of horses and dogs for the purpose. Their conclusions were: (1) The corneal reflex disappears before the last respiratory movement; (2) the head then becomes completely inert and the pupils dilate, with definite death; (3) resuscitation occurs when the perfusion is made

* *American Journal of Physiology*, 1906, xvii. 344.

without delay; (4) the perfusion should be done with oxygenated blood at suitable temperature and pressure, and should be sufficiently copious and prolonged; (5) resuscitation was possible only for very brief intervals under any conditions.

An idea of our observations is conveyed by the following condensed protocols of three selected experiments:

Protocol I.

PERFUSION WITH LOCKE'S SOLUTION.

Small dog, young. Ether; tracheotomy; cannula for injecting warm Locke's solution in jugular vein, connected with pressure bottle; cannula for bleeding in femoral artery; 400 c.c. to 500 c.c. of blood withdrawn.

About 700 c.c. of Locke's solution injected first time; then alternate bleeding and injection of Locke's solution until 1 litre had been injected. Corneal reflex still present when injection was stopped; reflex continued for a period of a few minutes, during which no fluid was withdrawn or added.

A second period of bleeding and injection of Locke's solution followed. Corneal reflex disappeared; then great dyspnœa and deep respiration. Heart stopped in twenty-five minutes from beginning of first bleeding; fluid escaping from femoral cannula still contained a fair number of red corpuscles.

Locke's solution, even when mixed with a considerable proportion of the animal's own blood, did not maintain the corneal reflex for any considerable length of time.

Protocol II.

PERFUSION WITH DEFIBRINATED BLOOD.

Pup. Ether; blood obtained from a dog on the previous day had been defibrinated and kept on ice for twenty-four hours was used for artificial circulation through brain.

11.23 a.m.: Tied right subclavian artery and vein; artificial respiration.

11.26: Tied aorta and put cannula in central end.

11.28: Tied inferior vena cava. Put cannula into inferior vena cava toward heart, running it up into auricle; corneal reflex present.

11.39: Tied heart in auriculo-ventricular groove, omitting the

great veins, and immediately began artificial circulation from a pressure bottle with the defibrinated blood prepared. Movements like dyspnœa, although defibrinated blood is circulating freely. Tested corneal reflex repeatedly, and found it well marked. Movements of the eyes occurred; pupils contracted.

11.47: Corneal reflex very feeble in right eye; good in left eye. Spontaneous respiratory movements ceased at this time.

11.48: Corneal reflex absent in both eyes; pupils strongly contracted. Tried for light reflex several times in last few minutes, but could not be certain of its presence.

Stimulation of vago-sympathetic nerve in neck caused dilation of pupil of right eye until 12.10; of left eye until 1.22. Corneal reflex was maintained for about nine minutes.

We concluded, from a consideration of the above data: (1) That solutions of the inorganic salts of the blood are totally inadequate to sustain the activity of the brain, including the medulla oblongata, either as regards reflex or voluntary function. Even when mixed with a considerable proportion of blood, these solutions are inadequate. (2) Defibrinated blood (oxygenated), circulated by means of a pressure bottle, maintained the activity of the reflex centres, and also of the cortical motor centres for short periods up to eight or nine minutes.

Protocol III.

Perfusion of Dog's Head with Entire Blood by Vascular Anastomosis to Another Dog. (*Cf.* p. 250.)

Two dogs, one somewhat larger than the other, were etherized. Tracheotomy. The peripheral ends of the carotid arteries and internal jugular veins of the smaller dog were anastomosed to the corresponding vessels of the larger dog. The skin-flaps from the neck were then sewed together.

4.35 to 4.36·30: Decapitated small dog in lower cervical region; respiratory movements ceased; no corneal reflex because of deep anæsthesia.

4.40: Respiratory movements of nostrils and mouth of transplanted head began; rate about 35 per minute. Corneal reflex obtained; pupils at nearly maximal dilation. Respiratory movements of transplanted head soon fell to 20 per minute. The depth of anæsthesia was reduced.

4.43: Rhythmic movements of upper eyelids of perfused head

apparently a little in advance of respiratory movements, but of same rhythm.

4.46: Movement of upper eyelids less rapid than respiratory movements of perfused head; well-marked corneal reflex.

4.47: Pupils at half-maximal dilation in transplanted head. More ether given.

4.51: Tried for light reflex of perfused head; probably not present.

4.57: Piece of meat pushed well back in throat of perfused head. Reflex movement of deglutition followed.

5.02: Pupils of perfused head smaller than at last observation.

5.07: No corneal reflex in perfused head.

Summarized, the protocol shows that movements of the eyelid were observed for about nineteen minutes. Corneal reflexes were maintained for twenty-seven minutes. Respiratory movements persisted for about thirty minutes, and were sometimes synchronous in both dogs. Swallowing movements were obtained. The results indicate activity of at least some of the mid-brain and medullary centres.

Thus it is seen that such a method of perfusion presents strong evidence of adequacy for studying the function of isolated organs. It must not be forgotten, however, that such perfusions may be made without direct anastomosis of the blood-vessels, as by connecting with oiled or paraffined tubes, or by anastomosing them by invagination. But the method by anastomosis, as previously described, seems to present certain points of superiority, as practical absence of danger of coagulation or stenosis, etc.

The ultimate results of transplanting organs and tissue masses by blood-vessel anastomoses are considered in another chapter.

As a brief consideration of further evidences of the inadequacy—or, indeed, even of the toxicity—of such solutions seem at this point to be timely, the following additional experiments are given, as they appear to have an important bearing upon this question.

A comparison of the behaviour of tissues capable of exhibiting easily observable responses to stimulation in blood and in artificial liquids is very instructive. Strips of heart-tissue from a turtle's ventricle are admirable for this purpose. When placed in the animal's own defibrinated blood, or in its serum, such a strip exhibits no contractile activity other than relatively slight tone changes; but in the commonly employed saline solutions well-marked

contractions as a rule soon appear (see p. 303). The relatively slight differences in the behaviour of the various solutions seem probably to be due to the different irritating values of the solutions themselves. That the irritating (toxic) properties of the solutions are associated with their physical characters is indicated by the fact that the addition of colloidal substances—*e.g.*, boiled starch—is followed by a decreased irritating power, for a ventricular strip placed in such a solution behaves as in blood. And, further, if this solution be replaced with colloid-free salt solution, the strip responds very much as though it had been bathed in blood. The irritating property may be said to be decreased, and characteristics similar to those of blood to be conferred upon the salt solution by the colloid.

The effect of such solutions applied to tissues during the operation of engrafting has been mentioned in connection with changes in engrafted vascular tissues (p. 104). But previously it has been observed that thin slices of thyroid exposed to the action of salt solution before being engrafted did not survive so well as similar slices treated with blood-serum. The observations on blood-vessels lead to similar conclusions.

The results obtained by perfusing the kidneys for a short time *in situ* with salt solutions give well-marked evidence of injurious action. This experiment (on cats) is followed in a large percentage of cases by the development of symptoms of uræmia, and death. Histologically, kidneys of such animals are found to have undergone profound alterations (p. 238).

Summarized, the results of such experiments show that—

1. Anæmia alone is apparently much less harmful than when accompanied by perfusion of any of the commoner salt solutions.

2. The commoner salt solutions do not seem to differ greatly in toxicity.

3. Attempts thus far to devise a non-toxic solution for perfusing —*e.g.*, salt-starch solution—have not been attended with any degree of success.

4. Anæmia with perfusion of the kidneys as a rule is followed by death of the animals within a few months, the majority dying in a few weeks.

5. The causes of the differences in time of death of the animals are unknown. Individual peculiarities may be (and probably are) an important factor.

6. Metabolic disturbances, seemingly in the direction of increased protein metabolism especially, occur.

7. Decrease in urinary secretion preceding death is probably an important factor to consider in interpreting the final symptoms, which are those of uræmic-poisoning.

8. Structural changes of a hæmorrhagic and degenerative character occur in the perfused kidneys.

It is interesting to consider if, with our present knowledge, a plausible explanation of this action can be given, since it is by such theoretical considerations that at least the practical aspects of an experimental investigation are advanced and a conception of the processes at least outlined.

In the case of simple anæmia, not only do the blood-vessels contain a fluid having normal physical properties for the cells of the kidney, but they also hold a certain amount of the pabulum for the kidney, including oxygen, in an available form. Also, they are suited to receive a certain amount of the metabolites thrown out by the kidney cells into the blood—*e.g.*, carbon dioxide—retention of which in the organ is detrimental. Further, absolute hæmostasis is difficult to accomplish under the condition of the experiment, so that renal products in the nature of "hormones" may still reach the general circulation, though, of course, in decreased amounts. However this may be, it must be concluded that the factor is in favour both of the simple anæmias and of the anæmias accompanied by perfusion, for it is well known that a tissue receiving a subminimal amount of blood (subminimal being used as indicating in the first instance an amount of blood too small to preserve the ordinary manifestations of activity—*e.g.*, in cerebral anæmia, etc.—and in the second instance that the blood is too dilute to preserve such manifestations) is easier to resuscitate than if the circulation be entirely stopped, or if the perfusion be carried out with a blood-free liquid; and that after resuscitation the normality of its subsequent activities will vary indirectly with the degree and period of anæmia. (*cf.* p. 338).

It is interesting at this point to note the work of Policard, who has reported in detail the results of an investigation undertaken with the view of determining what structural changes occur outside the body in the epithelial cells of urinary tubules under the influence of sodium chloride solutions of different concentrations. He decapitated white rats, quickly removed the kidneys and cut them into very small bits, the largest being under one millimetre in thickness. Such fragments were then immersed for fifteen minutes in salt solution of known strength at a temperature of 15° C. The

tissues were then fixed in formaldehyde solution, after which they were prepared for microscopical examination. He concludes that solutions of sodium chloride of all strengths (hypotonic, isotonic, and hypertonic) change more or less the cells of the convoluted tubules.

Now, if salt solutions are examined, it is found that they all contain one or more of the inorganic salts in approximately the proportion found in the blood. Yet they are all toxic. The same is true of the one containing, in addition to more abundant blood-salts—viz., sodium, potassium, and calcium—grape-sugar, which is considered another constituent of normal blood. In certain physical characters these solutions differ greatly from the blood, or even serum—*e.g.*, they are non-colloidal. Such being the case, we might attribute at least a part of their harmful influence to this factor. To test this point, a colloidal solution was prepared by adding boiled starch to a salt solution in such proportion that the freezing-point, electrical conductivity, and viscosity were nearly identical with normal cat's blood (defibrinated). Yet it was no improvement over the plain salt solution, as judged by the result (Cat 30, p. 277). But it would be a mistake to draw conclusions from this experiment, as starch is an abnormal colloid for blood. Besides, owing to the cooling of the kidneys during their exposure made for observing the course of the injection (room temperature was 15° C.), it is not improbable that the temperature of the solution was lowered to such an extent that its viscosity was increased. A considerably higher injection pressure was required than for the other solutions, so this, too, must be taken into account. Unfortunately, no control experiment was performed to determine the effect of merely introducing some of the solution into a cat's circulation.

Unlike blood, such solutions lack not only normal physical properties, but they cannot be considered to contain an adequate pabulum, there being no evidence that grape-sugar, which is a constituent of Locke's solution, is adequate in this direction, although it is destroyed by active tissues. Locke and Rosenheim, using surviving hearts, observed a more rapid disappearance of dextrose from the perfusion fluid during activity. McGuigan, working in my laboratory, obtained the same result for skeletal muscle prior to the appearance of Locke and Rosenheim's announcement (see p. 304). So long as the isolated skeletal muscles survive (as indicated by response to electrical stimulation), the sugar disappears. Later, the perfusion fluid filters through the walls of the blood-vessels into

the tissues, but the sugar contained therein does not appear to be destroyed. Still, since the period of anæmia is relatively short, and since organs, or even cells, like animals, undoubtedly contain a certain amount of material that for a time can take the place of that supplied by the blood, too much stress should not be laid on this point. Even a certain store of oxygen is laid up in the tissues themselves that can be drawn on in such emergency conditions, but there is no evidence that the kidney has a sufficient store to last any great length of time, as is the case in muscle.

Although the solutions employed in perfusing the kidneys were well aerated, they contained but a fraction of the amount of oxygen found in arterial blood—indeed, the amount even under pure oxygen is insignificant compared with ordinary venous blood. So it may be concluded that the tissues received too little oxygen. Again, the carrying capacity for carbon dioxide of such solutions is far less than that of blood; also, the total amount of solution injected into kidneys, compared to the amount of blood passing through them normally in the same length of time, is insignificant. We may conclude, therefore, that in anæmia with perfusion, as well as in anæmia alone, there is a profound disturbance of renal respiration, and that this is probably greater in the former than in the latter case. Although some blood probably entered the renal vessels and became mixed with the perfusion solution, the total amount thus entering, considering all other factors as being the same, would be less during perfusion, owing to the greater pressure of the perfusion liquid; also, such as entered the vessels and became mixed with the solution probably had a less metabolic value per unit, owing to the dilution. Numerous other possibilities might be brought forward, but what is written above is sufficient to indicate the state and complexity of the problem.

In the case of transplantation of tissue masses or organs with anastomosis of the blood-vessels, the facts presented regarding the toxicity of salt solution shed much light on the results, which have thus far in general been imperfect. But, as has been pointed out elsewhere (p. 196), under certain conditions we may hope for more satisfactory results when such operations are performed without perfusion of the blood-vessels with salt solutions, or, indeed, even without interruption of the circulation (p. 204). If this be realized, much information may thus be obtained, not only upon the functions and inter-relationships of different organs, but upon questions of heredity as well (p. 195).

By anastomosis of the blood-vessels of an isolated preparation with suitable blood-vessels of a closely related animal a liquid of optimum character (living, undefibrinated blood) may be employed, and optimum mechanical conditions for perfusion of isolated organs or tissue masses may be fulfilled. The superiority of this method of perfusion in certain respects is demonstrated by thus perfusing the brain, since preservation of evidences of activity of the lower cerebral centres indicates the fulfilment of the nutritional conditions in a high degree.

A method of uniting the vessels by suture for the purpose of perfusion, as practised above, approaches the ideal more nearly than any other method we have at present. By such a method the factor of coagulation at the point of junction of the two vessels, which usually occurs sooner or later when cannulæ are used, is eliminated. Such procedure, however, is not always possible, for it is sometimes desirable to make an anastomosis in a shorter period of time than that required for suturing the blood-vessels. In such an experiment as transplanting the head where a double blood-supply—two carotid arteries—is available, the anastomoses may be made without subjecting the engrafted head to any period of complete anæmia, for the vessels of one side may be anastomosed while the head to be engrafted is still receiving its own blood-supply. The factor of anæmia especially, introduces undesirable conditions when the perfusion is done for the purpose of studying the action of drugs upon the nervous tissues, for such tissues are highly susceptible to the injurious influences of anæmia. Recourse must then be had to other methods of re-establishing the vascular communication, which can be done in a shorter period of time. The most commonly employed method is the use of cannulæ. Although the walls of such cannulæ may be coated with oil or paraffin, coagulation usually sets in early. In such perfusion studies, therefore, it has usually been found advisable to make use of some coagulation retarding agent, such as peptone or leech extract. I have even obtained good results without the use of any such agents by employing short hour-glass-shaped, paraffin-coated cannulæ. Such anastomoses as I have practised were made between the common carotid artery and abdominal aorta, and the external jugular vein and inferior vena cava of dogs and cats. In such a procedure it is necessary to isolate as much of the vessels as is necessary to make the connection.

By such perfusion it is possible to study the physiological activity

of different parts of the body under different conditions. Such methods are especially valuable in studying the actions of drugs upon the integral elements of such a complex unit as the central nervous system. For example, Gaskell and Shore studied the action of chloroform upon the brain by joining the central ends of the common carotid arteries and external jugular veins of one animal to the peripheral ends of similar vessels in another animal. Thus, in one animal the brain and spinal cord were supplied by separate and distinct circulations. Then, by administering chloroform to the animal whose blood supplied the head of the other animal—the feeder—the effect of this drug on the brain alone could be studied.

Ryan and McGuigan have made use of a method of transfusion in studying the site of action of strychnine in the spinal cord. Their idea was to poison a limited region of the spinal cord with strychnine under normal circulatory conditions. In virtue of the anatomical connections of the cord elements, they were able to show that the irritability of the sensory or intermediate cells of the spinal cord was increased in mammals by strychnine. This was based on the observation that in such a condition of local poisoning spasms could be obtained in the unpoisoned region of the animal through stimulating the skin in the poisoned region. As illustrative of such transfusion methods, a brief statement of their technique and methods of study will be given.

Two animals were selected in the weight ratio of two and a half or three to one. Tracheal cannulæ were inserted. In the larger animal, or donor, a cannula was first inserted into the femoral vein, and was connected to a burette preparatory for the subsequent injection of peptone, which, however, was not injected until the dissection in the donor was complete. The two carotid arteries and one external jugular vein were isolated, and cannulæ inserted. With Y-tube connections the two carotid arteries were made to have a single outlet, which was to be connected with the thoracic aorta of the recipient. A rubber connection was also placed upon the cannula in the external jugular vein, which was to be connected to the inferior vena cava. All cannulæ and rubber connections were previously coated with a thin layer of paraffin. When the dissection was completed, an injection of 10 per cent. peptone in 0·9 per cent. sodium chloride solution was begun. The dose usually given was 0·25 gramme per kilo.

In the smaller animal—the recipient—the thorax was opened by

removing six or seven ribs on one side. Artificial respiration was given. Through the window in the chest wall the inferior vena cava and thoracic aorta were isolated. The vena azygos major and thoracic duct were ligated to prevent a subsequent spread of the strychnine from the lower to the upper parts of the animal.

Cannulæ were inserted into the peripheral ends of the thoracic aorta and the inferior vena cava. Connections were then made between the carotid artery of the donor and peripheral end of the thoracic aorta of the recipient, and the external jugular vein of the donor and inferior vena cava of the recipient. The period of anæmia could be reduced to two and a half minutes in making the connections. After the perfusion was begun, the pulse was strong in the posterior extremities of the recipient, the return circulation was excellent, and when the ball of the foot was incised it bled freely.

After the injection of appropriate doses of strychnine into the tubes between the donor and recipient, thereby poisoning the lower half of the recipient, spasms were first obtained in the lower region alone when cutaneous stimulation was applied in this region. In a short time stimulation of the skin in the poisoned region gave general spasms, while stimulation of the skin in the unpoisoned region gave only ordinary or no response. Spontaneous general spasms then ensued. At this period the spinal cord was severed at the level of the anastomosis. Spasms then continued in the lower half of the animal, but ceased above. Stimulation of the skin in the upper portion of the animal then gave only normal response, while stimulation below gave spasms confined to the lower half. Strychnine was immediately injected into the upper half of the animal, and was followed by typical strychnine spasms in the upper half. These observations showed that at the time of the initial strychnine-poisoning of the lower half of the animal, with manifestations of general spasms, the spasms of the upper part of the animal, when this region was unpoisoned, were due to influences which reached the motor cells from poisoned sensory cells, thus showing that the irritability of the sensory cells was increased by strychnine.

Many applications have been made of the method of transfusion in the study of biological processes, and as yet there remains a wide unexplored field.

Practicability of Operations upon Blood-Vessels.

Abundance of proof is at hand to show that suture, repair, and anastomosis of blood-vessels, from the experimental standpoint, is not only feasible, but relatively easy of successful execution under the conditions described.

Surgically, all the operations so tested have been entirely successful in both efficiency and permanency of function. In addition to the evidence obtained by clinical examination, such as good pulse, etc., and by direct examination of the tissues, such as very perfect union with smooth intimal covering and absence of stenosis, efficiency of vascular anastomosis was strikingly demonstrated. Twenty days after division and restoration of one common carotid artery, another dog's head was engrafted on to the neck by dividing the operated common carotid artery peripherally to the line of the anastomosis, and anastomosing the central end to the peripheral end of one carotid artery of the engrafted head. After anastomosis of the external jugular veins, the circulation was turned into the engrafted head, and, notwithstanding the fact that the blood had to pass through both the old and new anastomoses, the circulation was sufficiently adequate to bring about resuscitation in the engrafted head, with apparently a full return of consciousness, and to maintain it for several hours, or until chloroform was administered. Again, the results which Carrel and the writer have reported conjointly and individually, and the results of Watts and others, place the question of efficiency beyond doubt.

Permanency has been demonstrated in a large number of animals, and for different operations. For example, one of my dogs had a reversed circulation of arterial blood in one of the external jugular veins for more than five years; another dog, also in excellent condition, presents an active circulation through a carotid artery into which a segment of formaldehyde-fixed vena cava of another dog was engrafted more than three years ago. Again, a carotid artery of another dog, repaired in a similar manner with a segment of aorta from a rabbit, was functionating splendidly when the animal was chloroformed some seven months after the operation. Permanency of results in Eck's fistula in cats also has been mentioned (p. 101). Permanency, therefore, appears to follow all such successful vascular anastomoses, notwithstanding the occurrence in certain cases of profound anatomical alterations of the engrafted portion of the vessel.

Practicability is another important consideration from this (the surgeon's) standpoint. The simplicity of the operative procedures has been sufficiently dwelt upon elsewhere (p. 81).

All successful investigators in the field of vascular surgery have emphasized the importance of aseptic technique, and, of course, this should be followed in all vascular operations as in any other surgical operation. But emphasis upon this principle, from the standpoint of successful vascular suture alone, has been unduly insisted upon. For there is a mass of experimental evidence proving conclusively that blood-vessels may be not only repaired, but that the more extensive operations of end-to-end union of divided blood-vessels may be successfully accomplished with a non-rigidly aseptic technique. It is quite as essential for success to exactly carry out the mechanical features of the technique, especially as regards the accurate approximation of the intimal surfaces, and the infliction of minimal trauma. And for this there are good theoretical explanations. For example, owing to the flow of blood through the lumen of the vessel past the point of suture, and escape of blood outward from the vessel through the unavoidable suture trauma, any substances introduced into the wall of the vessel or into the lumen, if not too firmly attached, would be carried away. Also, owing to the well-known bactericidal action of the blood, both by phagocytosis and bacteriolysis, it tends to destroy any bacteria with which it may come in contact. And as such action presumably varies directly according to the quantity of blood coming in contact with the bacteria, it seems clear that such bactericidal action would be greater in the blood-vessels than in the tissues and spaces outside the blood-vessels. Furthermore, it is a well-established fact that the tissues of the blood-vessels are relatively resistant to suppurative influences. In witness of this may be quoted the well-known observations that in pulmonary tuberculosis blood-vessels may extend across cavities, resulting from necrosis of the lung-tissue with pyæmic infection and abscess formation, and adequately transmit the blood without leakage. Even the highly resistant tissues of the lung in this instance break down and disappear, leaving the tissues of the walls of the blood-vessels insufficiently damaged to cause rupture, although the supporting perivascular structures are absent.

Experiments published by Dorrance in 1906 show that surgical uncleanliness does not necessarily prohibit successful vascular suture. He employed a method similar to that described by

Clermont in 1901, which consisted essentially of the union of the vascular edges by means of a continuous suture of fine thread. Of a total of fourteen operations, twelve suppurated. Three of the operations were complete circular sutures. The specimens were examined from two to forty-two days after the operations. In two cases there was complete thrombosis, in five there were small thrombi, while in seven no visible thrombi were present.

The ease with which operative proficiency is achieved is one of the most pleasing features of the experiments; indeed, the ordinarily skilful surgeon readily masters it during his first operation. The manipulations appear to be vastly more difficult to the onlooker than they are in reality.

Of course, some means of producing temporary hæmostasis without much injury to the vessels is essential. The method by the use of ordinary serrefines or bull-dog forceps (p. 31) is recommended, but many other efficient and safe methods will occur to the surgeon. As previously described a simple method of compression with a coarse ligature or narrow strip of cloth used as a snare, with a short rigid tube to draw it through to hold it, and forceps, or with forceps alone to tighten and hold it, is always available during an operation, and may be confidently resorted to, as when suitable special forceps or other instruments for temporary vascular occlusion are not at hand. In fact, this method of compression has a number of good points in its favour that will readily occur to the surgeon.

For large to medium vessels (say down to those having a diameter of about four millimetres), No. 12 cambric needles (which may be obtained at any dry-goods store) will do, though for the smaller vessels smaller needles are better. For very small vessels, the smaller needles (Nos. 14 to 16) are necessary for the best results.

The suture material may be either hair (human hair is excellent) or very fine-fibred thread, such as silk. Ordinary sewing-silk is rather too coarse, but the finest and best grades of such thread may be employed by splitting before threading into the needles. A full account of the preparation of such needles and thread is given on page 24.

A ready source of material for repairing blood-vessels—as when segments are missing, or if for other reasons *e.g.*, retraction, it is desirable or necessary to lengthen the vascular tube—is the animal upon which the operation is to be performed. For example, on

the dog it is a simple and safe procedure to remove a suitable segment from an external jugular vein to restore the continuity of a divided common carotid artery; or a suitable vascular segment may be taken from another species. At least, all such hetero-transplantations thus far reported have given positive evidence of their efficiency; indeed, even when segments of blood-vessels are taken from cold-storage tissues, they may adequately serve such purposes (p. 10). But since there is no evidence that such tissues survive, and putrefaction and other processes—*e.g.*, autolytic—may occur in such tissues, thereby introducing the possibility of very grave complications—*e.g.*, blood-poisoning—if utilized for repairing blood-vessels; and since formaldehyde-fixed vessels serve the purpose, and are not open to the objection cited in the case of cold-storage vessels; and since there is no evidence that a cold-storage vessel can functionate superiorly to a formaldehyde-fixed one, I consider the use of cold-storage vascular tissues unwarrantable, excepting, perhaps, under very exceptionable conditions.

Perfectly fresh tissue from the same, or another individual of the same species, is recommended whenever convenient, as the maximum preservation of anatomical structure will be assured, particularly in the case of the autograft, and the mechanical factors for a perfect operation will be optimum. A fresh heterograft, or tissue taken from an animal of a different species, will fulfil the mechanical conditions quite satisfactorily, both as to operative manipulation and mechanical circulatory function. The formaldehyde-treated tissues will meet the operative conditions less perfectly, but success with such may be achieved without great difficulty, and the mechanical circulatory function has been quite satisfactory in our hands. From the results hitherto achieved it even seems possible that tissues not of animal òrigin might be successfully employed, but this must be established experimentally. So the operator has access to a wide assortment of reliable material.

It may be added that since such tissues are so readily obtainable, as at a slaughter-house, it would seem to be a practicable plan to fix and prepare a suitable supply for emergency use.

Results are, of course, the most important consideration. Since they have in large part been indicated above, it will suffice to say in conclusion that in my experiments *not one clinical symptom attributable to an operation solely upon a blood-vessel* has been observed to contra-indicate similar operations on similar animals for therapeutic purposes.

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CHAPTER VI

ANÆMIA AND HYPERÆMIA AND THEIR EFFECTS ON TISSUES

Anæmia.

THE effects of complete anæmia on tissues are so well known that it would be of small interest to devote much space to presenting them here. For example, death of tissues, as evidenced by the occurrence of gangrene after interference with the circulation, as in a limb, is well known even to the laity. But the phenomena following partial interruption of the circulation are not so well known or understood. Considered from this view-point, the subject becomes much more complicated, as factors appear that are hard to weigh individually and to balance one against the other. To illustrate: In complete and permanent anæmia, as when all of the vessels supplying a part are suddenly occluded, the circulation in the tissues supplied is immediately and completely arrested. The result is acute asphyxiation of all the tissues, for no tissue of the body can survive indefinitely in the total absence of circulation. The phenomena of asphyxial stimulation appear and disappear in different tissues in inverse proportion to the resistance of the tissues to anæmia. But a time will come when all evidences of vital activities have disappeared from all the tissues, and autolytic and other post-mortem disintegrative processes appear, leading to such phenomena as gangrene. Owing to differences in susceptibilities, such disintegrative processes develop more speedily in certain tissues than in others. In other words, the time of appearance of such processes varies indirectly with the susceptibility of the tissue to anæmia. Thus, a period of complete anæmia sufficient to destroy the vitality of tissues of the central nervous system, as tissues of the brain, may not have any noticeable lasting effect upon the tissues of an extremity, as tissues of the foot. Similarly, in all tissue masses there are certain elements which may survive a period or degree of anæmia that may have proved

fatal to other elements. And between the extremes of perfect survival and complete extinction of vitality, tissues showing grades of injury, but capable of survival, may be present. In other words, a tissue mass may present survival phenomena of comparable character to those observed in the head of an animal which has been submitted to a period of anæmia.

The writer's views on this subject are based to a large extent upon such observations, and an account of some experiments involving cerebral anæmia has been given in another division of this work (Chapter IX.).

The phenomena of incomplete anæmia are no less interesting than those following complete anæmia, nor are they of less importance. For this form of anæmia is not only of much commoner occurrence, and the conditions leading to its production more complex, but the vital reactions are such that it is much more difficult to understand and interpret them than the phenomena following permanent complete anæmia. To discuss the matter, it is first necessary to consider the question of what constitutes a normal circulation in order that there may be no misunderstanding as to what constitutes anæmia.

All, perhaps, will agree that three factors must enter into any consideration of blood-supply—namely, unit of blood per unit of tissue per unit of time. Also, that the composition of the blood and the demands of the tissue have to be taken into account. Even from purely theoretical grounds this must be so, for the blood and its circulation may be considered as being for the purpose of supplying conditions essential to the respiration of tissues. That a given mass of tissue requires a given quantity of blood may be deduced from the fact that a large animal contains more blood than a small one. That a certain composition of the blood is necessary is indicated by the results following severe hæmorrhage with replacement of the blood lost with an equivalent volume of salt solution—*e.g.*, beyond a certain degree of hæmorrhage the life of a higher animal cannot be saved by infusion of salt solution alone.

Observations upon the composition of blood in disease lead to the same conclusion—namely, that alteration of the composition of the blood below a certain point is incompatible with health or even life. This is very clearly illustrated by a form of bovine malaria known as blackwater or Texas fever. The normal composition of the blood may be determined, and then the animal inoculated with the organisms producing the disease. This may be done

either by means of infected ticks, which readily attach themselves to the skin, or by a subcutaneous injection of blood from an "immune" individual; for such an animal is immune only in that it carries the disease in a chronic form, and so long as this condition lasts, a reinfection gives rise to slight or no objective symptoms.

Now, as the disease develops in the susceptible animal, the blood may be studied from day to day. Taking the percentage of blood sediment as shown by centrifugalization as an index of the oxygen-carrying capacity—for this and the hæmoglobin content run parallel—as the disease progresses the oxygen-carrying capacity of the blood decreases. When this has fallen to one-fourth of the normal or less, which is not uncommon in severe cases, although the temperature may have returned to nearly normal, the animal may, after slight over-exertion, suddenly present alarming symptoms of deficient tissue respiration which may terminate fatally with well-marked symptoms of anæmia, particularly of the central nervous system. Such a result, of course, is due to a complexity of factors. But it may with reason be assumed that the abnormally low respiratory value of the blood, of which the hæmoglobin content is an index, is a very important factor. For conceding that what commonly is termed failure of the circulation supervenes, this is attributable at least indirectly to the condition of the blood. For the heart will continue to beat so long as it is supplied through its coronary arteries with blood of adequate composition, and it will maintain an adequate pressure in the aorta, and hence in the coronary arteries, to circulate a sufficient amount of blood in a given time to sustain itself, provided a sufficient peripheral resistance is present. Now, the peripheral resistance is largely maintained in the intact animal by nerve impulses transmitted from the vasomotor centre situated in the upper end of the spinal bulb. So when the nervous tissues comprising this centre fail, as under inadequate circulation, the arterioles dilate and permit the blood in the large arteries to pass more rapidly into the capillaries. Also, the viscosity of the blood is less than normal, so it flows with greater ease through the vessels. But this factor tends to work both ways—that is, though it tends toward a lower blood-pressure, yet with a lower pressure a larger amount of blood will pass through a given vascular area in a given time than would be the case with blood of normal viscosity. To meet the condition of decreased vasomotor tone, the heart responds by endeavouring to pump the blood more rapidly into the aorta. But unless vascular tone is

soon restored, the heart is not able to maintain a pressure in the aorta adequate to send enough blood through the coronary vessels to sustain its own activity, especially since it is in a state of overwork, and therefore demands a hypernormal supply of blood. The result is that the heart will soon begin to fail and the pressure to sink below the point compatible with an adequate circulation, so the animal dies. And in the instance cited, since the tissues in general are in a weakened condition from the ravages of the disease, this result is accelerated. But the probable initial cause of the train of events is anæmia of the vasomotor centre. For not only has it been subjected to the deleterious conditions set up by the disease, but, owing to the demands of the tissues for more blood, due amongst other conditions to the decreased respiratory value per unit volume of blood and their increased respiratory demand per unit of tissue mass, as indicated by the fact that the total oxidations in the body per unit of time are increased during the disease (fever, emaciation, increased urea output, etc.), the centre has been called upon to adjust the circulation to the needs of the tissues to the best advantage under the circumstances, perhaps letting more blood into the capillaries of an organ here, and decreasing the amount in a correspondingly capacious capillary tract elsewhere, yet all the while maintaining a total peripheral resistance adequate to permit the heart to work to best advantage. The tissues being in what may be considered an abnormally high state of oxygen hunger, and owing to their increased production of carbon dioxide and other metabolic products, they demand an accelerated circulation to supply more oxygen and to remove end-products.

So the respiratory centre in the quiescent animal is probably working to near its maximal capacity under the adverse conditions. Yet, when through increased muscular activity a greater demand is made for blood, it endeavours to respond. The ratio between respiratory demand and respiratory supply changes in such a way and to such a degree that the centre breaks down, and general dissolution follows.

Now, gathering these and other complex factors together, it would seem that under normal conditions the amount of blood of normal composition circulating through a unit mass of tissue per unit of time may be taken as the starting-point of a physiological conception of blood-supply. A given tissue mass requires more blood in a unit of time in a state of activity as compared with a state of rest. As indicated in the pathological condition described

—Texas fever—in which a prominent feature is a decreased hæmoglobin content, and hence a deficient oxygen-carrying capacity, in a state of activity the circulatory apparatus may become inadequate to make up for this deficiency by sufficiently increasing the amount of blood. So, though the circulation may be good as regards the mechanical factor of rate, the respiratory needs of the tissues are not sufficiently well met to preserve the tissues in an adequate functional state, so the mechanism fails. In harmony with the known relative susceptibility of tissues to anæmia, the part of the circulatory mechanism comprised within the central nervous system is first to go. After this occurs, decline is rapid. For in the absence of that vascular tone which is controlled by the centre, the peripheral resistance decreases until the heart is no longer able to maintain an adequate blood-pressure—*i.e.*, its own blood-supply automatically falls away until it cannot maintain the output of work required of it.

Before leaving this aspect of the subject, it is interesting to again note how the alterations in the composition of the blood, as after hæmorrhage and saline infusion, or in the diseased condition, automatically favour a greater circulation with the same pressure. That is, in such conditions—conditions accompanied by a decreased respiratory value per unit of blood—the viscosity decreases, and as a result the blood flows with less resistance through the vessels. Thus the tendency is to maintain the normal ratio between unit mass of tissue and the respiratory value of the blood circulating through it in a given time by increasing the rate of flow.

Returning to the question of what constitutes anæmia, it may be said that the condition results when the amount of blood passing through a unit mass of tissue in a given time falls below that required for the normal requirements of the tissue in its given state of activity. What this is in actual terms of weight or volume is not known. And from the nature of the conditions it would be a difficult matter to measure it accurately. But by taking the circulation time of certain organs, together with the amount of blood they contain and their weight, and the ratio of blood weight to body weight, it is possible to obtain approximate quantitative values for a few tissues. For example :

Using the approximate figures employed by Professor Stewart in calculating the work of the heart, the average amount of blood passing through a gramme of tissue of a man in one minute would be about 0·06 c.c. But since it is known that the vascu-

larity and circulation time of all tissues are not the same, it is obviously impossible to consider this figure in any but a general way. Furthermore, in the case of organs having two sets of blood-vessels—viz., nutritional and functional, such as the heart, lungs, and liver—it would manifestly be erroneous to include the circulation through the latter type of vessels in a consideration of anæmia or hyperæmia of such tissue from the standpoint under discussion.

But merely to illustrate, we may say that 1,000 grammes of tissue require on the average about 1 c.c. of blood per second. And since arterial blood loses approximately two-fifths of its oxygen in passing through the capillaries—that is, about 8 c.c. per 100 c.c. of blood, since 100 c.c. of arterial blood contains about 20 c.c. of oxygen—the average volume of oxygen required by a given mass of tissue is roughly expressed by taking 8 per cent. of the blood passing through the tissues. For example, if 1,000 grammes of tissue be supplied with 1 c.c. of blood per second, then it follows from what has just been said that 1,000 grammes of tissue is supplied on an average with about 0·08 c.c. of oxygen per second.*

It would be interesting to consider the minimal circulation that will supply the needs of certain of the tissues. But little is known upon this point. It is, of course, obvious from what is known of the differences of resistance of different tissues to anæmia that great differences will be found in different tissues. It is probably safe to say that if the blood-pressure is suddenly reduced by one-half, a derangement of the higher intellectual processes will result, which would indicate that the minimum circulation necessary for certain cerebral functions is about one-half of the normal. In the case of the kidney, it has been observed that the secretion of urine stops when the blood-pressure is reduced to about one-third of the normal. The heart continues to beat with a somewhat lower pressure. These three tissues are mentioned merely as representing different types. But it is not absolutely necessary that we should have quantitative values for the practical application of the conceptions in meeting such conditions clinically, for such conditions are met symptomatically with success. In many cases the life of the animal is saved, not by treating the symptoms, but by treating the condition in such a manner that acute symptoms do not appear. In other words, treatment is directed with the view of maintaining a safe ratio between respiratory demand and supply. By merely leaving the animal alone, and seeing that it is not called upon for

* *Cf.* Stewart, "Heart," 1911, iii. 33.

undue muscular effort, the respiratory demand will be minimized. Of course, every rational effort is put forward to maintain the respiratory value of the blood within safe levels through both its composition and circulation. For example, in extreme hæmorrhage, ideal treatment theoretically would be the introduction of suitable living blood into the vessels with the view of making up the respiratory deficiency both as regards composition and circulation. For increasing the mass automatically improves the circulation, for it tends to make the blood fit the vessels—a fundamental requirement in the maintenance of an adequate blood-pressure.

Conditions leading to anæmias may vary widely in nature. As pointed out, decline in normal amount or composition of the blood, if sufficiently great, leads to the condition. If the circulatory mechanism fails, even when the blood is normal in amount and composition, the result is the same. Both conditions lead to general anæmia in the physiological sense, simply because the respiratory demands of the tissues cannot be met. Local anæmia results from a variety of conditions. It is assumed that the blood and the heart are adequate to supply the tissues in general within normal limits. Yet, for some reason, some region, such as a limb or a gland, is insufficiently supplied with blood. As a rule this condition results from arterial obstruction, as in arterial thrombosis or embolism. This affects particularly the relatively large branches. But such is not always the case, for the arterioles and even the capillaries may become obstructed, as in anthrax infection, where masses of the bacilli have been demonstrated in the smaller vessels of the kidney. External pressure may also obstruct arteries. The smaller vessels, particularly the capillaries, are especially subject to this form of occlusion, for the pressure of the blood within them is less than in arteries. Their walls are thinner and less rigid, and, owing to their small size, a relatively slight diminution in the cross-sectional area of their lumen retards the blood much more than in the case of the larger vessels. That is, owing to the physical laws of the flow of liquids through tubes which are applicable to the flow of the blood through the vascular system, the velocity in all but the smaller vessels is said to vary directly with the diameter; while in the smaller vessels, and especially the capillaries, it varies with the square of the diameter. Aside from this, it is obvious that a force acting through a distance sufficient to completely obliterate the lumen of a capillary would have no appreciable action if exerted on the wall of even a small

artery—say, one measuring 1 millimetre in diameter, for a capillary does not ordinarily exceed $\frac{15}{1000}$ to $\frac{20}{1000}$ millimetre in diameter.

The arterioles may become so constricted through nervous influences that at least only a subnormal amount of blood may pass through them. And this has been offered as the explanation of certain pathological processes, as in Raynaud's disease. Also the action of certain agents or substances carried in the blood or applied locally may produce similar circulatory effects. A well-known example of the first class of substances is ergot. Of agents acting locally, cold, adrenalin, cocaine, and the like, are examples.

Obstruction of the veins likewise leads to anæmia in the sense that it reduces the amount of blood passing through the part to an abnormal degree. It is true that more blood will be present in the tissues in a unit of time, but less will circulate through them (anæmia with congestion). And though pathologists term the condition "passive hyperæmia," the term "anæmia" is the correct one in the physiological sense. If a ligature be slowly tightened and tied about a member, since the veins are more superficially situated and are more easily compressed than the arteries, the return circulation will be hindered before the outgoing, and the limb will contain more blood than a non-ligated limb. But notwithstanding that it is hyperæmic in the pathological sense, it is anæmic so far as its vitality is concerned. And the proof of this is that it will quickly die. A method of treatment in vogue among surgeons is the production of such a condition by means of an elastic ligature —the celebrated stasis hyperæmia. Neither the arterial nor the venous circulation is completely restricted. But for the reasons just given, the venous flow is relatively more restricted than the arterial, so a condition of partial anæmia is produced. The effect of this is to dam the blood back in the veins and in the capillaries, which raises the pressure in both. The blood circulates more slowly, and as the greatest respiratory interchange between the extravascular tissues and the blood takes place through the capillaries, and as, relative to the mass of blood, the area of vascular endothelium—which is said to carry on its metabolic commerce with the blood in the lumen of the vessels—is greater in the capillaries than in the arteries, the blood within the capillaries must become quickly impoverished and loaded with products of metabolism. This may be hastened when the ratio between tissue demand and supply becomes altered through the

impoverishment of the blood to the extent that the tissues are stimulated to greater activity by the onset of asphyxia (see p. 184).

Owing to the dependence of the capillary endothelium upon the blood for its nutrition and for the carrying away of waste products, and since more work is thrown upon it by the increased blood-pressure, it must at a relatively early stage suffer derangement of function. And this is the case. It is possible that it makes an effort to contract in response to the stimulating action of asphyxia. And if the pressure within the capillaries is not too high, it may succeed in narrowing the lumen to a degree, for it is known that certain capillaries have contractile properties; but whether such contraction occurs under the conditions being considered is not known. In any event, the capillaries will soon become widely distended. And that their normal properties are affected is strongly indicated by the abnormal passage of liquid from the blood through their walls into the surrounding tissues—that is, the phenomena of œdema, which soon appear. Now, if at some such stage the impediment to the circulation be removed, more blood will circulate through the part than normally, due to the widening of the channels. And hyperæmia is initiated, which is of the character termed " active " by pathologists.

Cupping is another method employed for inducing hyperæmia. But it, too, at least—as commonly performed—produces results very similar to those produced by temporary constriction of the veins. The partial vacuum, acting upon the skin, mechanically causes a congestion of blood in the vessels of the region; and as the negative pressure overtops the resistance of the capillaries, they become distended and engorged with blood. But the rate of circulation decreases under such circumstances, and anæmia very soon results. After the cup is removed, a state of accelerated circulation follows. This applies with a high vacuum cup. With a vacuum that is not sufficient to overcome the capillaries, an increased circulation might occur from the beginning.

In reality, then, such procedures must be considered as acting primarily in many cases by causing a state of partial asphyxiation. And since it is known that in general, where such asphyxial measures are adequate to reduce sufficiently rapidly the arterial circulation, the view that asphyxia may be used to urge sluggish tissues into greater activity is not wholly without foundation. This view harmonizes also with the clinical results of such procedures, which on

the whole indicate an increase in tissue activities, as the union of a refractory fracture, or healing of a sore, or the overcoming of an infection, or the reduction or disappearance of an overabundant or abnormal tissue, as a bone callus, or a neoplastic growth. In the latter example the relative susceptibility of tissues to asphyxia is also possibly a factor (*cf.* p. 104).

A number of operations have been proposed and carried out with the view of producing benign circulatory alterations in pathological states. Thus, Widal reported the results of a lateral anastomosis between the portal vein and the inferior vena cava in a case of a man suffering from hepatic cirrhosis. Death occurred three months after the operation. Peritoneal adhesions between the omentum and the abdominal wall have been produced with the view of establishing collateral circulation between the portal and

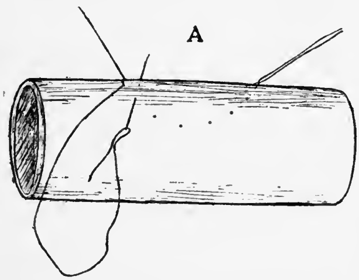

FIG. 75.—POSITION AND DIRECTION OF STITCHES IN PRODUCING A PARTIAL VASCULAR OCCLUSION.

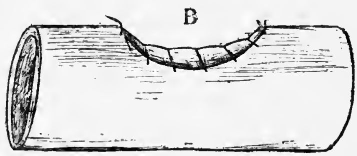

FIG. 76.—OPERATION OF PARTIAL VASCULAR OCCLUSION FINISHED, SHOWING FLAP FOLDED AND BOUND DOWN ON EXTERNAL SURFACE OF VESSEL.

the systemic circulation in cases of hepatic cirrhosis. And from the latter operation (omentopexy) particularly good results have been reported (Osler). Of a similar character is Edebohls' renal decapsulation operation for Bright's disease, which has for an object the establishment of new renal vascular connections. Also surgical operations have been devised with the view of producing a beneficial effect in pathological conditions by decreasing the blood-supply. Perhaps the best-known example is the ligation of the thyroid arteries in goitre. But for anatomic and other reasons it is not always permissible to completely occlude the blood-vessel, and therefore operations have been devised and performed with the view of altering the blood-supply to the part by partial occlusion of the arteries.

With Carrel, the writer has successfully produced partial arterial

occlusion by placing a few continuous stitches through the artery as shown in Figs. 75 and 76 The results of such an experiment are given in the following protocol by Watts, who tested the method :

Partial Occlusion of the Aorta.

May 14, 1906.—White and yellow shepherd-dog. Abdominal incision. Aorta exposed a short distance above its bifurcation, and its lumen narrowed by several through-and-through sutures.

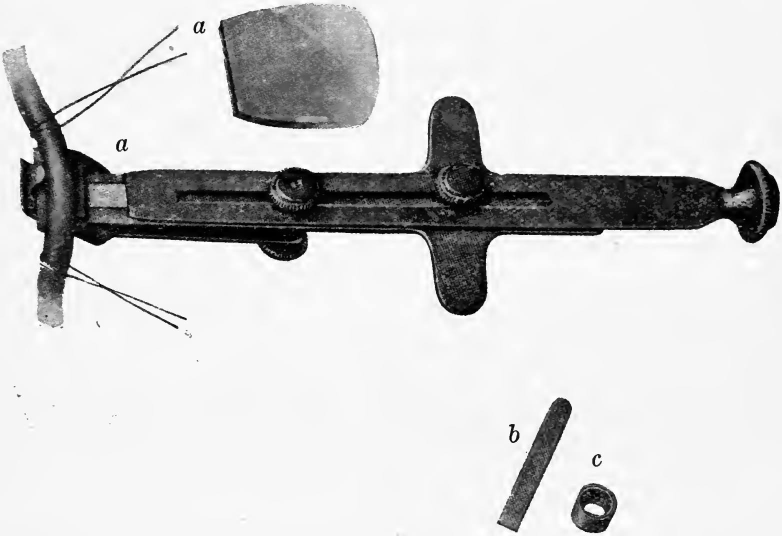

FIG. 77.—THE ORIGINAL BAND ROLLER IN THE ACT OF CURLING A METAL STRIP ABOUT AN ARTERY. (HALSTED.)

a, The tip of the driving blade, enlarged ; *b*, the metal strip ; *c*, the band slightly tightened with the fingers as when a degree of incomplete occlusion is desired. The proportions depicted are those observed at the time the drawing was made. We should now regard the length of the metal strip as about one-third too great for its width as well as for the size of the artery represented.

After the suture was completed the pulsation distal to the suture was considerably diminished. Wound closed with silk. No dressing.

May 23, 1906.—Dog in good condition. Healing *per primam*.

June 23, 1906.—Dog anæsthetized, and specimen removed. Lumen of aorta diminished to half its normal size by the sutures. Many of the sutures projected into the lumen, and were covered with a thin layer of organized fibrin.

Another method of partial arterial occlusion is that experimentally

developed and later introduced and applied by Professor Halsted, which essentially consists in the partial occlusion of vessels by means of encircling aluminium bands. The technique is best described in his own words, and is as follows :*

"The aluminium, usually purchased in sheets of about twenty-five degrees of thickness (American scale), should be cut, before being rolled down to the thinness desired, into strips of convenient length, and of width not greater than three-quarters of an inch. If much wider, the strips warp inconveniently, and have to be cut to waste in the selection of flat and regular parts for band material. It is well to stamp each strip with the numbers indicating the thickness of the metal, and to have on hand a liberal supply of the various thicknesses from No. 25 to No. 46. The finest numbers we have used on the very small femoral and renal arteries of the dog. In the average dog, for the abdominal aorta, Nos. 34 to 35 are suitable; and for the thoracic aorta, Nos. 33 to 34 we have used most frequently. In the human subject, for the abdominal aorta below an aneurism near its bifurcation, No. 33 sufficed; but ordinarily a heavier size would be required. For the common iliac, No. 32 answered the purpose admirably; for the thoracic aorta, Nos. 22 to 25, perhaps; for the common carotid, we have almost invariably selected No. 33. The length of the band should be almost that of the circumference of the full artery. The width varies from about 2 millimetres for the renal arteries in the dog to about 1 centimetre for the thoracic aorta and innominate artery in man. The figure depicts a band suitable for the human carotid and for the average dog's aorta. The band in this illustration we should now regard as too long for its breadth by approximately one-third. It is best to sterilize the aluminium only once. It may become too brittle for perfect rolling by repeated boilings. When rolled down on the artery enough almost to obliterate the pulse, a band of seemingly proper dimensions has rarely described more than two complete circles. The filing or 'manicuring' of the band is of very great importance. It should be curved like a finger-nail at the forward end, and at the other cut precisely at right angles to its long axis. With a file the edges should be made perfectly smooth, but not sharp, and the rounded end symmetrical. A carefully filed band coils more easily both in the instrument and under the fingers, and, what is more important, is not likely to cut the artery. The aorta is the only vessel that I have seen cut itself on the band, and then,

* *Journal of Experimental Medicine*, 1909, xi. 378.

with the exception, perhaps, of two very young dogs or puppies, only when the band was badly filed or clumsily rolled, as in the early experiments, especially those in which forceps were employed to supplement the work of the fingers in tightening the too broad and too heavy bands at that time employed. Silk ligatures, even when occluding the aorta only partially, have in my experiments repeatedly cut entirely through the aorta, and without causing the death of the animal. They may leave in their wake various forms of diaphragm which more or less obstruct the lumen of the artery (see Fig. 80).

"**The Band-Curler.**—The original instrument (*vide* Fig. 77) had, we soon discovered, three major faults. It was—(1) too broad at the arterial end; (2) the band lacked anterior support, as it was

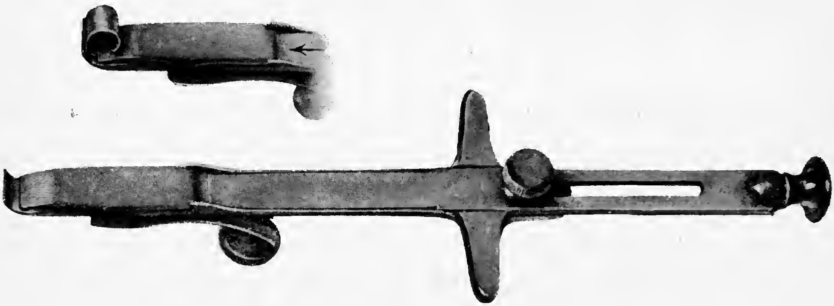

FIG. 78.—THE IMPROVED BAND ROLLER—THE SIZE USUALLY EMPLOYED IN EXPERIMENTAL WORK. (HALSTED.)

The instrument shown in full length is unloaded. In the abbreviated cut the band is about to be expelled from the roller. This band is broad enough for the abdominal aorta in man, and the diameter of the circle is too short for a vessel requiring such a broad band.

being pressed onward by the driving blade *a* (magnified *a′*); and (3) the latter did not always engage the former, owing to the fact that it was too springy and was insufficiently linked to its fellow on which it glides. To remedy the tendency for the band to buckle forward, one was compelled to support it with the finger during the process of curling. This was occasionally a difficult and usually an awkward performance."

The other figure "shows an improved and satisfactory band roller or curler. In the full-length drawing the instrument is not loaded; in the abbreviated sketch the band projects from the end half curled. The principal defects of the old instrument have been remedied in the new. Buckling of the band is prevented by the boxing. The driving-plate cannot spring away from its fellow, and

the width of the instrument has been sufficiently reduced to permit it to be passed freely between the closely given off branches of the abdominal and thoracic aortæ. When the thinner bands are used it is sometimes necessary to give the faintest tip backwards to each of the two right-angled corners of the band to insure its engagement in the downward thrust of the piston or driving-blade. After it has encircled the artery the band may, if its corners have been bent, be freshly squared with the scissors before being curled tighter by the fingers. This is not, however, necessary. The curler being armed with the carefully filed band of correct proportions,

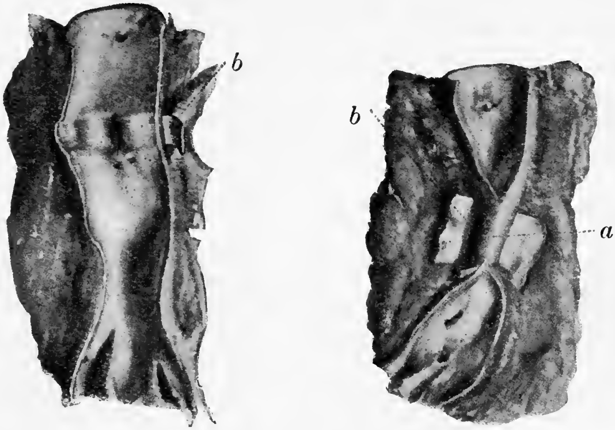

Fig. 79.—Aorta of Dog after Partial Occlusion by Band for One Month. (Halsted.)

The band (*b*), in outline, is seen through the vessel's wall. Aorta of dog converted into a solid cylinder (*a*), the band (*b*) having embraced the artery for three and one-half months.

the plunger is made to engage the band and to force its convex end into sight before the instrument is passed under the artery. In the first figure the act of curling the band about the artery is shown, after the old manner, in its first stage. As the curling proceeds, the instrument is gradually withdrawn. In arranging for the tightening of the band, its convex end should lie on the wall of the artery, and be overlapped by the square end. With a very little practice one learns to avoid bending or flattening the band in the process of tightening it. The band should be long enough to encircle the artery in the expanded state of the latter, and the metal should be sufficiently thick and wide to sustain the curl given it. If perfectly rolled, the inside and outside circles of the

metal touch each other at all points of the surface of contact, and in consequence, the cohesion force is greatest. The artery should be raised from its bed by two tapes held far enough apart to leave uncovered sufficient free space on the artery for the occupancy of the band. Traction on the upper tape should be made to interrupt the blood-current, and thus to reduce the size of the vessel. A

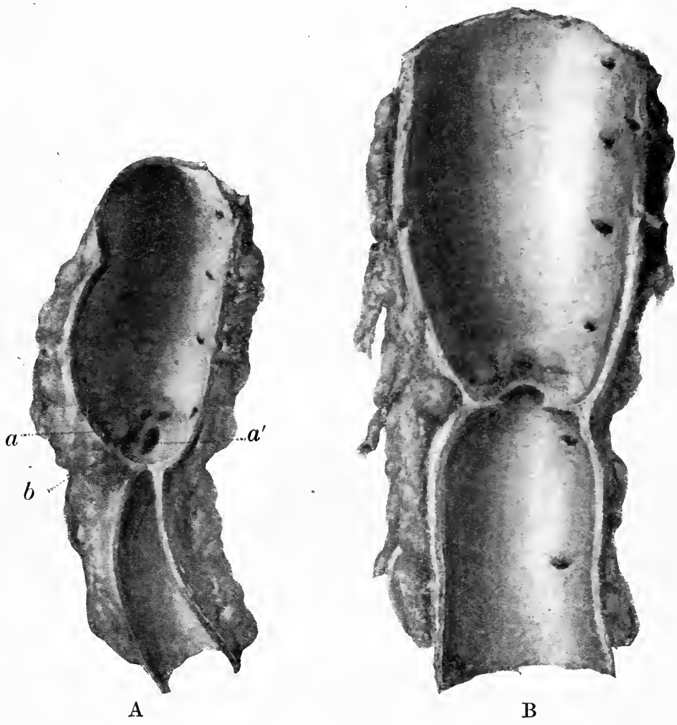

FIG. 80.—AN AORTA ABOUT WHICH A PARTIALLY OCCLUDING LIGATURE OF SILK HAD BEEN PLACED. (HALSTED.)

In A, the wall of the artery is divided anteriorly only enough to expose the diaphragm formed in the track of the ligature and perforated by two holes, *a* and *a′*. The silk ligature, at *b*, is more plainly seen in B, in which the diaphragm has been divided as far as and into the anterior perforation.

band-curler should be selected which might make the metal describe a circle smaller than the distended or full artery, but a little larger than the empty one ; then, with the return of the blood-current, the artery expands and may fill the band quite snugly.

"After complete occlusion of the abdominal aorta the femoral pulse does not usually return for weeks, or even months ; and

after incomplete occlusion of the thoracic aorta the femoral pulse may be hardly discernible after seven months. The anastomotic circulation takes place through the vasa vasorum, as discovered and so beautifully depicted by Luigi Porta ; and by way of the internal mammary and epigastric arteries, as especially emphasized by Kast. We have repeatedly observed the great increase in the vascularity of the abdominal wall, particularly on splitting the recti muscles, but also in making mid-line incisions at operations subsequent to the one at which the band was applied " (*cf.* Cooper).

The clinical symptoms of aortic occlusion observed in a cat were similar to those described by Halsted in dogs. A cat showed partial paralysis of the hind-limbs for a few days following severe traumatism of the aorta just posterior to the renal arteries, but this soon entirely disappeared. On the twentieth day the animal was killed with chloroform, as its kidneys were desired for examination. On examining the aorta, the lumen was found to be completely occluded by an old thrombus beginning 2 to 4 millimetres posterior to the origin of the renal arteries, and extending backward for 11 to 14 millimetres (Fig. 44, p. 69).

Halsted stated at the time his article was written that the aluminium band had been successfully applied in man to the common carotid artery twelve times, and once each to the thoracic aorta, the abdominal aorta, the common iliac, the femoral, and the innominate arteries.

It would seem, therefore, that the partial occlusion of the arterial lumen may be readily and safely accomplished by either of the methods described. But perhaps the stitching method is superior to the metal-band method in being simpler.

To determine whether the large arteries can be occluded long enough to make it possible to observe the effect of the arrest of the circulation in the territory supplied by the occluded vessel, without irreparable damage to the artery during the period of occlusion, Matas with Allen have carried out a large series of observations on dogs by compressing the large arteries, as the femoral and carotid. They employed the principle of Halsted's method—namely, occlusion by means of metallic bands. Several forms of bands were tried, but finally bands made of strips of No. 20 sheet aluminium were employed.

They describe the method as follows :

These bands are cut long enough to be used as aneurism needles, bent and curved in the shape of a flat hook, which can be readily

insinuated between the blood-vessel and its sheath. After the band has been carried around the circumference of the vessel, it is gently compressed by the fingers of the operator until the pulse on the distal side becomes imperceptible. The excess of band which remains is cut off with stout scissors, or preferably small wire-clippers.

In placing the bands around the small arteries of the dog in attempting complete occlusion it is very easy to crush them and set up traumatic changes not directly due to the use of the band. To avoid this, one end of the band is doubled on itself, arranged somewhat like a clothes-pin, and the vessel slipped down between the opposing surfaces of the band until the pulse can no longer be felt. The excess of band is then cut away. In this way danger of crushing by excessive force is reduced to a minimum.

Each band should be prepared for use by paring the sharp angles of the free end that is to be carried around the artery with scissors, and the sharp edges should also be softened with a file.

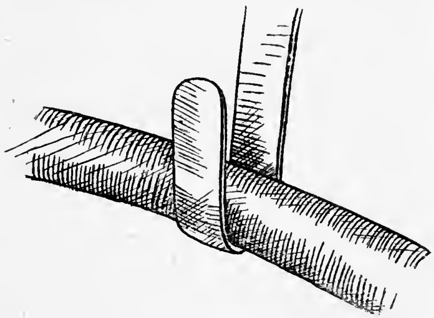

Fig. 81.—Mode of Applying Aluminum Band to Atery. (Matas and Allen.) (*Jour. of Amer. Med. Assn.*, 1911, lvi. 234.)

If it should become necessary to remove the band at any time, on account of ischæmic disturbances in the territory supplied by the occluded vessel—*e.g.*, when cerebral disturbances occur after occlusion of the common carotid—the point of a sharp instrument inserted between the approximated ends of the band and slightly twisted accomplishes the separation and releases the vessel, allowing the circulation to be restored.

The bands have now been applied in the human subject fourteen times: to the right common carotid and right subclavian (third division), for innomino-aortic aneurism; to the right common carotid and right subclavian, for innomino-carotid aneurism; as a preliminary to extirpation of a tumour of the upper carotid region, followed in three days by simultaneous extirpation of the tumour with the common carotid, including its bifurcation; to the right common carotid, as a preliminary to extirpation of tumour of the lower jaw and submaxillary region; to the left common carotid, as a preliminary to extirpation of pharyngeal, palatine, and tonsillar neoplasm;

to the right common carotid and right subclavian, for innomino-aortic aneurism; to the internal and external carotids, just above the bifurcation, for innomino-aortic carotid aneurism; to the right common carotid, for aneurism, involving carotid bifurcation; as a preliminary to extirpation of parotid tumour; to the right common carotid and right subclavian, for innomino-aortic aneurism; to the left common carotid, as a preliminary to extirpation of carcinoma of neck, jaw, and cheek; to the right common carotid, as a preliminary to extirpation of carcinoma of the root of the tongue; on the common carotid, to control bleeding and starve a carcinoma of the right parotid region. In all these cases the bands were applied as "test occlusions," but as in no instance did cerebral or other disturbances in the peripheral circulation develop, the bands were allowed to remain undisturbed, and in this way permanently occluded the vessels to which they were applied (p. 68).

In all cases the perfect tolerance by the tissues of the band, when properly applied, was demonstrated. Without exception, the bands remained permanently encysted in a fibrous sheath without causing the slightest irritation.

An interesting observation was made by Charles Mayo on carotid occlusion in a woman. Twenty years previously one common carotid artery had been ligated; also the patient had suffered the loss of an eye. He used a strip of tin, and applied it to the artery under local anæsthesia. Near the end of the operation the patient remarked that she could not see anything—"the light was going out." He immediately began to loosen the clip, and vision returned. Six months later the clip was still on the artery, and vision was said to be better than before the operation.

Professor Matas reported some interesting observations on a patient after occlusion of one (left) of the common carotid arteries. The vessel was occluded by means of an aluminium band applied under local anæsthesia. The band was moulded and pressed on the vessel with the fingers until the pulse on the distal side disappeared. Careful note had been taken of the pulsation of the opposite carotid and of the pulsations of the facial and temporal branches, which were distinctly felt. After the occlusion it was noticed that the temporal and facial pulses on the operated side had practically disappeared, while those on the non-operated side remained as before. During the operation no symptoms of cerebral anæmia were noted. The pupils remained symmetrical, there was no syncopal feeling or dizziness, and only a little pallor on the affected side.

The patient, a man sixty-two years old, stood the operation well, and before the wound was closed drank a toddy with relish.

No unfavourable symptoms were noted until about seven and a half hours after the operation, when it was discovered that he had become aphasic and very somnolent, and presented almost complete right hemiplegia. The stupor became coma-like, and vomiting and marked dyspnœa occurred. The pulse was 120, and weak. All the manifestations came on rather suddenly. About an hour and a half after the cerebral symptoms were recognized the band was removed from the carotid, which restored the circulation in the distal portion of the trunk and branches. This readily occurred, the pulse fell to 90, and the respiration improved. The following day the patient, though aphasic, became more lucid, and the hemiplegia decreased. He swallowed well, and maintained a good state of nourishment. On the succeeding day there was a decided improvement, and on the day following the mental condition was practically normal, and aphasia and all paretic symptoms, save a slight numbness and tingling in the arm and leg on the side that was paralyzed, had disappeared.

Matas and Allen believe that in two out of fifteen cases of carotid occlusion practised by them grave cerebral complications were avoided by the timely removal of the compression.

Crile states that in operations on the head and neck he has temporarily occluded the carotid artery more than 150 times. In younger subjects he has rarely observed unfavourable symptoms, but in older ones he has seen rather marked symptoms, such as slight delirium for a day after a carotid occlusion of an hour and a half in a patient over seventy years old. Allen remarks that "the nearer the patient to forty-five years of age, the greater the danger of closing either of the carotids" (*cf.* p. 314).

It would seem, therefore, that the partial occlusion of the arterial lumen may be readily and safely accomplished by any of the methods described.

Matas some years ago performed successfully an operation for the treatment of aneurism based upon the gradual occlusion of the artery at the site of the aneurism. In order to produce this condition, after shutting off the circulation on either side of the aneurism he opened the sac, and sutured all openings into the arterial channel. Next, he folded and sutured together the excess of the aneurismal bag. On removal of the temporary hæmostatic clamps the restricted circulation was confined chiefly

to the main arterial channel. Owing to the extent and nature of the operation, gradual occluding thrombosis occurred; but owing to the gradual character of the occlusion, the establishing of an effective collateral circulation was favoured.

After ligation of the main artery of an extremity, there is at first a disappearance of pulsation in all the branches. This will remain absent until such time as the circulation is re-established directly through the vessel or by enlargement and development of collateral branches. This can take place with great rapidity after ligation of a large trunk, as the femoral. The return of pulsation in the large vessels below can occur, it has been said, as early as twenty-four hours in the young, and proportionately later in older persons (Thoma). The veins play an important rôle in the re-establishment of such collateral circulation, so that, when the vein and artery are both occluded, the danger of death to the extremity is much greater than when only one of them is occluded (*cf.* Cooper).

Guthrie states that he had had many opportunities of seeing the vein and artery of a limb divided by a wound or included in a ligature, but rarely had he seen a case in which mortification did not ensue; and he was disposed to consider it as a general rule, liable to an occasional exception, that where the femoral artery and vein are divided or included in a ligature, the limb will be lost by gangrene.

Age, as above stated, is a great factor in the establishment of an efficient collateral circulation. It is held that the collateral circulation is more active in the young than in the aged. It is probable, also, that differences exist in individuals and in species.

Halsted completely occluded the abdominal aorta of a dog, and noted temporary weakness of the hind-legs; but one month after the operation he described the animal as being "perfectly well and active." Two months after the operation the femoral pulse was detected for the first time. Eleven days later the pulse was countable, but still very small. This and other similar observations (p. 147) emphasize the importance of not attaching too much significance to the absence of the pulse itself in deciding upon an amputation.

Factors Involved in the Establishment of a Collateral Circulation.

The factors concerned in the re-establishment of an adequate blood-supply to a part after the normal circulation has suffered diminution are varied. For the exact mechanism of such restora-

tion varies somewhat with the nature of the condition leading to the anæmic state, as when the arteries are obstructed, or when the veins are obstructed; and with the degree of completeness of the anæmia, as when a tissue mass is completely isolated from the circulation, as compared to a partial obstruction of the vessels.

Establishment of collateral circulation after partial arterial obstruction is the more frequently observed—as, for example, after ligation of an artery, such as the ulnar. In such a condition physical factors immediately enter into play. Owing to the shutting off of the blood through the artery, the pressure in the capillaries tends to fall, and as a result the velocity of the blood in the radial artery will tend to become accelerated, for the velocity varies directly as the ratio of the pressure behind to the pressure before increases. For example, the mean pressure of the blood in the aorta before ligating the ulnar artery may be equal to the pressure exerted by a column of mercury 120 millimetres in height, while the arteriole pressure may be equal to 40 millimetres of mercury. The ratio of aortic to arteriole pressure would be in such case as 3 is to 1. After tying the artery, the aortic pressure will not vary. The pressure in the arterioles supplied in part by the ulnar artery will tend to fall when the artery is occluded, owing to the decrease in the blood entering them. Let it be supposed, for the sake of illustration, that the arteriole pressure falls to 30 millimetres of mercury. Then the ratio of aortic pressure to arteriole pressure in the affected part would be as 120 to 30, or as 4 to 1. Immediately, then, the velocity of the blood in the radial and other collateral arteries will become correspondingly accelerated. And if the cross sectional area of such vessels be sufficiently great, only a very short period of deficient capillary circulation will result. But if this is not the case, a deficient circulation will ensue. If this is inefficient to permit the tissues to carry out their normal functions, but is adequate to sustain the metabolism above the point incompatible with survival, the function of the part will show more or less derangement. In this condition other emergency circulatory mechanisms are brought into activity (*cf.* Guthrie, 1830).

In such a condition paralysis of the arterioles and capillaries would lower the resistance to the passage of blood through the tissue, thus favouring an increase in the supply both by accelerating the rate of entrance from the arteries and by increasing the capacity of the capillary area, lengthening the period of

sojourn of the blood in the tissues. Also, the reflex vascular nervous mechanism may be thrown into a state of activity in the direction of increasing the diameter of the vessels.

A widening of the lumen of the patent arteries to the part may occur, thus increasing the supply of blood. The mechanism of this action may be of a reflex nervous character, for it is known that even the large arteries possess such a mechanism.

The possible mechanisms involved in the establishment of efficient circulatory conditions in a part after obstruction to the venous return are also numerous. An immediate effect of such obstruction is the damming back of the blood in the capillaries and arteries. This results in a heightened capillary pressure, which may be so great as to distend the capillaries at once. Though more blood than normal quickly appears in the part, it very rapidly loses its arterial character. So, if the venous circulation be markedly restricted, the blood in the capillary tract soon becomes highly venous. Under these conditions the tissues in the restricted area rapidly pass into a state of asphyxiation, their functional activity declines, and the part becomes cold.

If the condition is produced by tying one or more of the veins from a part, such as the foot, enough circulation may be maintained to sustain the life of the tissues; but the circulation may be inadequate for the normal functioning of the part. In such a case, either through damming back of the blood and increasing the capillary pressure, thus causing a widening of the capillaries; or slowing the capillary circulation to such an extent that, through deficient nutritive processes the capillaries dilate; or through a direct or reflex nervous process the capillaries dilate—room for more blood is made in the part. And this for a short time will tend to maintain a blood-supply for the tissues. This, however, is adequate for only a transitory period in maintaining the tissue activities. But so long as the venous restriction is maintained, it permits of a very thorough removal from such blood as enters the tract of substances required by them. The patent venous channels are distended by the blood they are required to transmit—that is, blood from the areas ordinarily drained by them, and blood from the areas deprived of their normal venous channels, which through anastomotic connections is diverted into them. In response to the increased demand made upon them, their capacity increases, so an efficient venous flow from the restricted area may become established.

In the case of both arteries and veins, under the conditions con-

sidered, it is possible that new vessels are formed; for when a small mass of tissue is entirely removed from the body and is replaced under suitable conditions, blood-vessels grow into it. So it may survive, and not only preserve normal histological structure, but it may, through growth, enlarge many times in size. This may easily be observed by removing a fragment of an ovary or testicle from a young fowl, and engrafting it beneath the skin in proximity to a large blood-vessel. Owing to the transparency of the fowl's skin, the graft can be observed from day to day, and within a fortnight it is not uncommon for visible vascular connections to appear. As the period of sexual maturity approaches, the mass of tissue rapidly enlarges, and the blood-vessels correspondingly increase in size.

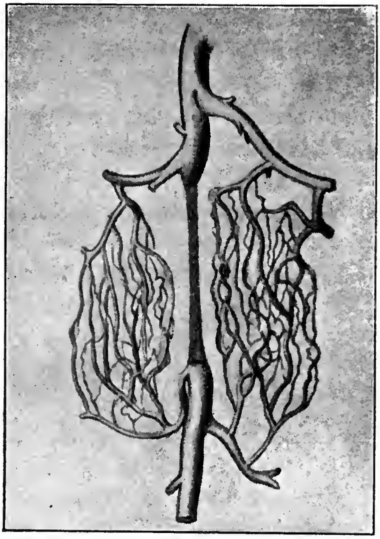

Fig. 82. — Collateral Circulation after Ligation. (Marwedel.)

Indeed, the fact that the blood-vessels of tissues that show great periodic variations in functional state, such as the ovaries and uterus, undergo corresponding morphological alterations, illustrates in a very convincing manner the extremely great adaptive power of blood-vessels to the demands of tissues. But the mechanism by which such changes are wrought is as yet in a but little experimentally explored field.

The subject of the establishment of collateral circulations may be summarized by saying that, following partial occlusion of arteries or veins to an extent compatible with life, an effort is made by the vascular system to correct the defect. Some of the processes through which this is accomplished are known, and some are unknown. And the same is true of the development of new vascular connections as to an engrafted tissue.

Hyperæmia.

Hyperæmia is, roughly speaking, the opposite state to anæmia. That is, it occurs when a unit mass of tissue in a unit of time is supplied with a unit mass of blood whose metabolic or calorific or

other value is greater than that demanded by the tissues in the same period. Active hyperæmia in this sense is a purely hypothetical condition, for, so far as the writer is informed, no instance is known in which a tissue receives more blood in response to its demand than it utilizes.

The results of an increase in the circulation upon tissues will vary with the state of the tissue and the nature of the condition leading to increase in the circulation. In the case of a resting tissue going into a state of functional activity, the resulting augmentation in the circulation through the part may be looked upon as of an active hyperæmic character, but not as a true hyperæmia. The result of the condition is an increase in metabolism and in the functional output of work. Anabolic and katabolic processes will become augmented, but the algebraic sum of the two will leave a balance in favour of katabolism. In other words, the stored-up energies of the tissues will tend to be depleted. And if the anabolic processes are incapable of meeting the katabolic demands, the state known as fatigue will result—that is to say, conditions arise which tend to cause the tissue to diminish its katabolic activities. This results in what is termed the "resting-state." Circulation to the part will after a time subside, so that when through anabolic processes the tissue has been restored to its non-fatigued resting condition, the circulation will be but adequate for the minimal state of activity.

The changes occurring in such a condition are chemical, mechanical, and histological. For example, more oxygen is taken in and more carbon dioxide is given off. Work is performed as indicated by a muscle lifting a weight or by a gland raising a column of liquid by pressure of its secretion. Structurally, cellular changes, such as the disappearance of cytoplasmic granules, changes in the cell outline, etc., may be observed.

In the case of a hypernormal functional state of a tissue the picture is the same as that just described, with the difference that under certain circumstances an increase in the tissue elements—that is, hypertrophy—may occur; for example, enlargement of the thyroid lobe remaining after excision of its fellow. But such a result cannot be attributed directly to the increased circulation, for the blood is merely passive, the increased supply being in response to the demand of the tissue. The materials only, and not the influences leading to the hypertrophy, come from the blood.

In more strictly pathological states, where tissues demand increased blood-supply, the results are varied. Great abnormalities of function and structure occur. But the rôle of the blood is merely a passive one, for the demand for an acceleration of the circulation and the conditions—at least, in some instances, as in the development of greater vascularity—together with the influences governing the activity of the tissue itself, originates outside the blood-vessels.

Views regarding the result of mechanically increasing the circulation through a part—that is, producing passive hyperæmia—are not altogether harmonious. For example, if the vasomotor nerves to a part be cut, the vascular channels will dilate, and a greater quantity of blood will flow through the part. Greater growth has been observed under such conditions. But although the existence of specific trophic nerve influences is doubtful, if not disproved, it is still possible to object to these results as being due directly to the increased circulation, as it might be due to some change set up in the tissues themselves by cutting the nerves, for when a nerve is sectioned, nerves other than the vasomotors are always severed.

Assuming that no such nervous trophic influences are concerned in the phenomenon, it by no means follows that the result is due to a better nutrition of the part from the presence of a greater circulation—that is, one cannot conclude that the growth of a tissue may be augmented by merely supplying it more abundantly with blood, for in meeting conditions necessary to accomplish this an abnormal state of the capillary circulation is inevitable. And it is possible that this in itself, acting either directly, as by pressure upon the tissue elements, or indirectly through changes taking place within the capillaries themselves, will result in an alteration of the normal function, and in stimulating the tissues to greater activity. For example, such an hyperæmic state is usually, if not always, accompanied by an increased pressure within the capillaries. This condition might favour the passage of substances used by the tissues out of the blood more than it would the entrance into the blood of waste products from the tissues. Thus the accumulation of waste products might serve as a stimulus to the tissues, and an abundance of food materials being supplied at the same time, it is conceivable that hypertrophy might result.

Again, it might be urged that, owing to the greater amount of blood flowing through the part, the temperature of the part would

be increased, and owing to the increase in temperature, the tissues might manifest a greater activity. That this last view may be the key to the explanation is indicated by the fact that some of the best observations of this character have been made upon external structures, such as rabbits' ears and cocks' combs, where the actual increase in temperature may be considerable. For if such an experiment be performed upon the ear of a rabbit, a very marked difference in the temperature of the two ears may be perceived even by the hand.

The Effect of Vascular Anastomoses upon the Circulation.

Depending upon the character of the operation, the effect of vascular anastomoses may range from *nil* to converting a vein into an artery, and *vice versa*. After repair of a simple injury in a vessel wall, unless marked constriction is produced, but slight circulatory disturbance results. And the same is true after reunion of a divided vessel, either by direct end-to-end anastomosis, or by the interposition of a suitable segment of another vessel, even though the latter has lost its vitality. But if an artery and vein be divided, and the central end of each be anastomosed to the distal end of the other, very great alterations in the circulation ensue.

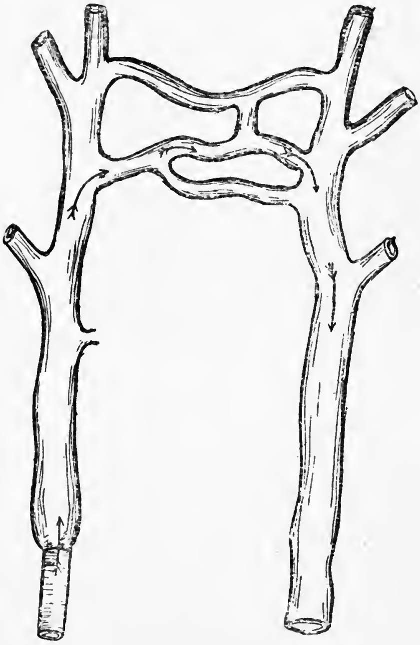

Fig. 83. — Showing Anastomosis of the Central End of a Carotid Artery to the Peripheral End of the External Jugular Vein and the Free Anastomotic Connection between the External Jugular Veins (Dog).

If the central end of an artery is anastomosed to the peripheral end of a vein, the result is that the velocity of the blood in the arterial portion of the vessel will be greater than normal (see p. 78), for the blood empties directly into the vein; and owing to the freer anastomotic connections between veins, the peripheral resist-

ance will be less than in an artery. So not only will the velocity in the artery be greater, but the pressure will be lowered. In the venous portion of the vessel the direction of the circulation is the reverse of normal, the pressure is higher, and the blood is arterial. The pressure in the capillary area normally drained by the vein will be increased, for not only has the vein ceased to transport venous blood away from the capillaries, but it has engaged in conveying arterial blood to them. So the capillary pressure is raised, not only by the damming back of the blood owing to the vein having ceased to convey venous blood (passive anæmia), but by the vein leading more blood into the part. Some of the blood sent back through the vein no doubt may reach unobstructed venous trunks through direct anastomotic connections. And these quickly respond to the new condition, and rapidly enlarge to accommodate more blood passing to veins in returning to the heart. So the greatest increase in capillary pressure due to the presence of the reversal of the direction of the circulation in the vein would be observed shortly after the operation. And experimental observations bear this out, for when the central end of one common carotid artery is anastomosed with the peripheral end of the inferior thyroid vein on the opposite side of the neck, the effect upon the circulation in the gland is immediate and striking, particularly if the gland presents the condition of well-marked goitre—that is, if it be markedly enlarged and the blood-vessels prominent (see Protocol of Dog 16, p. 169). On occluding the vein preparatory to division and anastomosis with the artery, the gland may swell somewhat and become purplish—that is, present the appearance of passive anæmia or engorgement with venous blood. But very quickly after the new circulation is established it greatly enlarges in size, and the blood-vessels become more engorged, but very red or arterial in hue. The whole mass presents strong systolic expansion, and very soon the tissues become markedly œdematous. After a few days the swelling begins to subside, and in less than a fortnight the gland is probably no larger than at the time of the operation. But it does not stop here; it continues to contract, and becomes smaller and denser. This goes on until after some months the gland mass may approach in size a normal thyroid lobe in an animal of similar species and size. If such a gland be examined histologically, it will be found to be densely fibrous and decreased in vascularity. But the thyroid tissue present appears to be more normal in arrangement and in staining reaction

than at the time of the operation, if the gland at that time was goitrous.

By anastomosing the peripheral end of an artery that has free anastomotic connections, as the common carotid, to the central end of a vein, the circulation in the artery becomes reversed and the pressure is lowered. While in the vein the pressure may be raised and the blood becomes of arterial composition, but direction

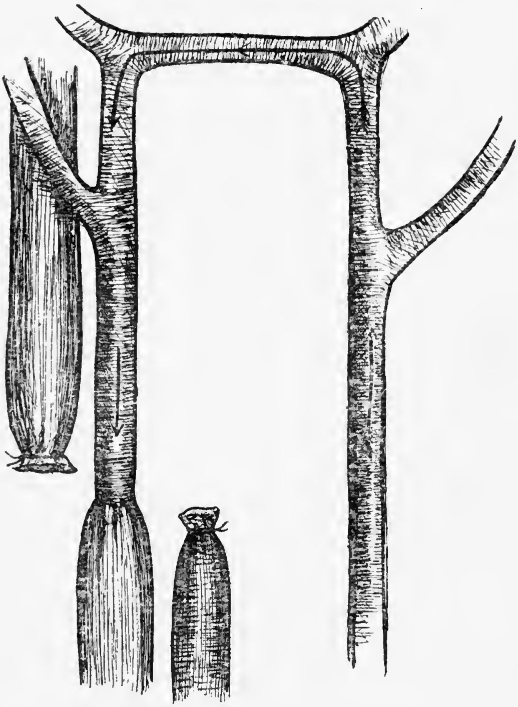

Fig. 84.—Direction of Circulation after Anastomosis of Peripheral End of Right Common Carotid Artery to the Central End of the Right External Jugular Vein.

of flow remains normal. Under such circumstances, tissues supplied with arterial blood from the peripheral portion of the artery may be rendered partially anæmic—at least, for a time—owing to the decrease in arterial supply, and the tissues which normally are drained of blood by the vein may become congested and present symptoms of congestive anæmia, owing to the increased venous pressure.

If the central ends of an artery and vein be united, the same

conditions hold as regards the vein, only they are magnified. In the case of the artery the pressure falls and the velocity of the blood is accelerated.

If the peripheral ends of an artery and vein be united, the resulting circulatory changes will depend to a large extent upon the

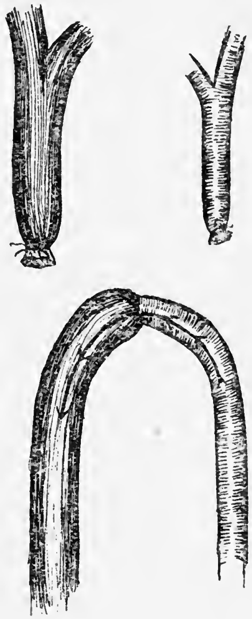

Fig. 85.—Direction of the Circulation after Anastomosis of the Central Ends of an Artery and Vein, as the Carotid and Jugular.

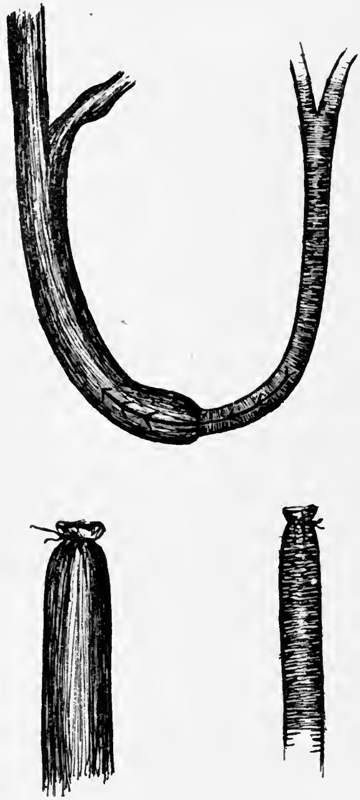

Fig. 86.—Direction of the Circulation after Anastomosis of the Peripheral Ends of an Artery and Vein, as the Carotid and Jugular.

nature of the artery. If it be of the character of the common carotid, in so far as anastomotic communications are concerned, the circulation in the arterial tract will become reversed. The pressure will be lowered. Likewise a reversal of the direction of the circulation in the vein will follow, and it will become of arterial character and the pressure will be increased.

If proximal or distal ends of like vessels be united, as the peripheral or central ends of the common carotid arteries or external jugular veins, at least the portion of the trunks will contain more or less stationary blood, and changes in pressure may occur.

If the principal artery and vein to a part be divided, and a double anastomosis made consisting in the union of the central end of the artery to the peripheral end of the vein, and *vice versa,* and if the collateral circulation is relatively weak, a reversal of the circulation in the part may be accomplished. (This is complete, as when an organ is extirpated and then replaced, and such arterio-venous anastomoses performed, p. 246.)

Such an experiment was published by Carrel and the writer. The femoral vessels of a hind-limb of a young dog under ether anæsthesia were exposed and divided, and the central end of the

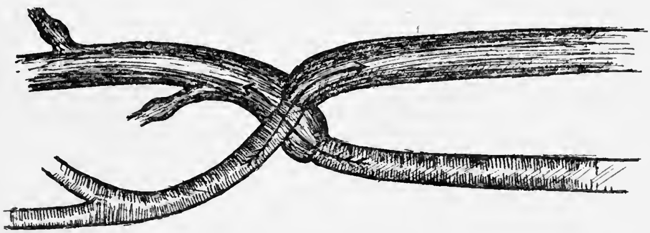

FIG. 87.—DIRECTION OF THE CIRCULATION AFTER DOUBLE ARTERIO-VENOUS END-TO-END ANASTOMOSIS, AS IN THE FEMORALS.

The direction of the circulation is reversed in the peripheral end of both artery and vein.

artery united to the peripheral end of the vein. The vessels below the anastomosis were exposed, so that they could be directly observed.

Immediately after the operation the arterial blood distended the femoral vein, but did not pass the valves. Fifteen minutes later blood in the main trunk of the vein became red, while the blood in the saphenous and other superficial veins of the leg and foot remained of venous character. Arterial blood was soon observed to enter the mouth of the saphenous vein and to displace the dark blood, driving it in the reverse direction to the normal flow in veins. About thirty minutes after the operation the peripheral portion suddenly became red, due to the entrance of arterial blood. An hour after the operation blood allowed to escape from the peripheral end of the artery was red, but it showed dark streaks. An hour later blood similarly allowed to escape showed a larger

percentage of blood of venous character. Three hours after the operation the femoral and saphenous veins and most of their branches, including the veins of the foot, were of arterial colour and pulsated like arteries. The femoral artery presented a venous colour, and blood drawn from it contained but a few streaks of arterial hue. Four hours after the operation the reversal of the circulation in the limb was very extensive.

So far, what has been said applies to vessels of the general circulation. In considering the effects of operations upon such vessels as the portal vein, all circulatory peculiarities are to be taken into account in analyzing the results.

It is a deplorable fact that not only has the notion been advanced that in conditions in which an increase in the circulation of a part is indicated, as in a limb presenting evidence of deficient circulation, it would be a good plan to make a lateral anastomotic com-

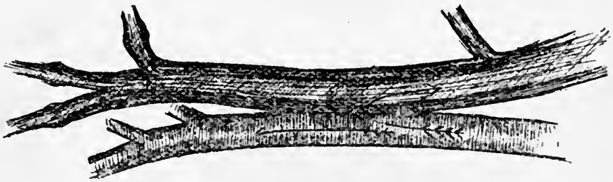

FIG. 88.—DIRECTION OF CIRCULATION AFTER LATERAL ANASTOMOSIS BETWEEN AN ARTERY AND VEIN, AS THE FEMORAL.

Swelling on branches indicates location of valves.

munication between the principal artery and vein in order to accelerate the circulation to the tissues, but it is claimed that such an operation has been performed; and the result was precisely what might have been expected—loss of the limb.

Lateral anastomotic communications between arteries and veins would in general lead to—(1) an increase in the velocity of the blood in the central portion of the artery; (2) decreased pressure and circulation in the distal portion of the artery; (3) increase in the venous pressure, with admixture of arterial blood and acceleration of the circulation through the central portion of the vessel; (4) slowing of the circulation through the distal portion of the vein; and (5) decrease in the capillary circulation of the affected part, due to decrease in arterial pressure and increase in venous pressure. In short, the tissues are rendered anæmic both by decrease in arterial supply and increase in venous pressure.

Hyperæmia has been experimentally and surgically produced in

organs and tissues by interruption of nerve pathways as by the division of nerve trunks or extirpation of ganglia. Removal of the cervical sympathetic ganglion is a type of the latter operation, and is followed by dilation of the blood-vessels of the head and neck supplied by nerve fibres supplied through this ganglion.

A partial denervation operation performed by Dr. Carl Beck, of Chicago, upon the kidney of a woman presenting evidences of renal insufficiency gave interesting results. Before the operation 180 c.c. of urine containing less than 2 gms. of urea was excreted in twenty-four hours. After the operation the amount of urine in twenty-four hours arose to 550 c.c., which contained 15 gms. of urea. Two weeks later the amount of urine for the twenty-four hour period was 1,000 c.c., and the amount of urea was about normal.

But it is, of course, obvious that such operations are by no means to be regarded as without possible undesirable sequelæ, for it is known that degenerative processes are prone to follow the destruction of nerves.

Hyperæmia, by reversing the circulation in veins by arteriovenous anastomosis, is considered in the following chapter.

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CHAPTER VII

THE EFFECT OF ALTERATION OF THE CIRCULATION ON GOITRE

THE effects of tying arteries supplying an organ are so well known as to need no mention, save to say that in general, if the arterial circulation be decreased beyond a certain degree, atrophic processes are induced in the tissues affected. The operation has been applied in the surgical treatment of goitre, and though not above reproach, seemingly favourable results have been observed. But such an operative procedure is hazardous in principle. For to obtain the desired therapeutic condition it is necessary to affect materially the circulation. And since the shutting off of too large an amount of circulation is liable to lead to undesirably extensive retrogressive processes or even death of the affected tissue, and since the only sure test of the degree of partial circulatory decrease is to obtain the result, to predict the exact result in a given case is uncertain. And from the inconstancy of the results, the operation, though conservative as compared with promiscuous extirpation of thyroid tissue, is not satisfactory. But the surgeon who practises ligation of the thyroid arteries with the view of inducing the gland to return toward a normal condition is to be commended above the surgeon who removes the gland; for the former endeavours to cure a pathological state, and leave his patient whole, while the latter removes an organ necessary for normal existence, and leaves his patient a cripple for life. No surgeon will remove a broken leg because it is useless until all efforts to save it have been exhausted; and amputation will be performed only when to delay would certainly endanger the patient's life. Yet, since the leg is not a vital organ, to amputate in the beginning would be simpler, and might not shorten the patient's life—only leave him a cripple. And with a cork leg and hypertrophy of his sound limb the patient after a time would manage to get about quite well. But is there a surgeon in the whole world who would advocate amputation for all frac-

tures? Though to some such a comparison of a goitre to a broken leg may appear extreme, I am confident they are the exception. In the first place, the thyroid presents no evidence of being a vestigial structure, and even if it did, this would be but a weak argument to justify its removal. For so-called vestigial structures are known in certain instances to be very necessary to well-being. As an example, the pituitary body may be cited, thanks to experimental investigation, especially noteworthy being the brilliant results of Cushing. On the other hand, the thyroid presents both anatomical and functional evidences of being an active and very necessary vital organ. It is as unreasonable to argue in justification of its removal in disease from the fact that an animal can live without it as it would be to argue for the removal of the stomach for gastritis from the fact that the patient might live without that organ. In both instances organs designed for other purposes take up the burden of the sacrificed member and carry it after a fashion.

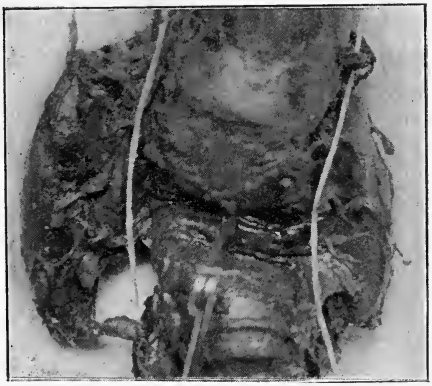


Fig. 89.—Enlargement after Reversal of the Circulation in the Inferior Thyroid Vein to a Normal Thyroid Lobe of a Dog Six Days after Operation.

The operation was performed on the right side.

But the burden in addition to its own may be too great, so the activities of the organism as a whole will be reduced to a corresponding level; and the result is an abnormal functional state. To recapitulate in order to avoid being misunderstood: The thyroid gland is as necessary to a normal state as a limb; and in pathological states its removal should be given the same consideration as an amputation, and all rational conservative measures should be exhausted before deciding upon a removal operation in either case.

With the thyroid, such conservative general measures include personal hygiene, dietetics, medication; and local measures include external applications of various kinds, intraglandular injections, section of nerves, ligation of arteries, reversal of the circulation in the veins by arterio-venous anastomoses, and ligation of veins. It is chiefly the latter two measures that will be dealt with here.

In 1905, with Carrel, the writer began the investigation of the effect of reversing the circulation in the thyroid veins by arterio-venous anastomoses on goitre. From a consideration of the results, the writer was impelled to extend the observations and to study

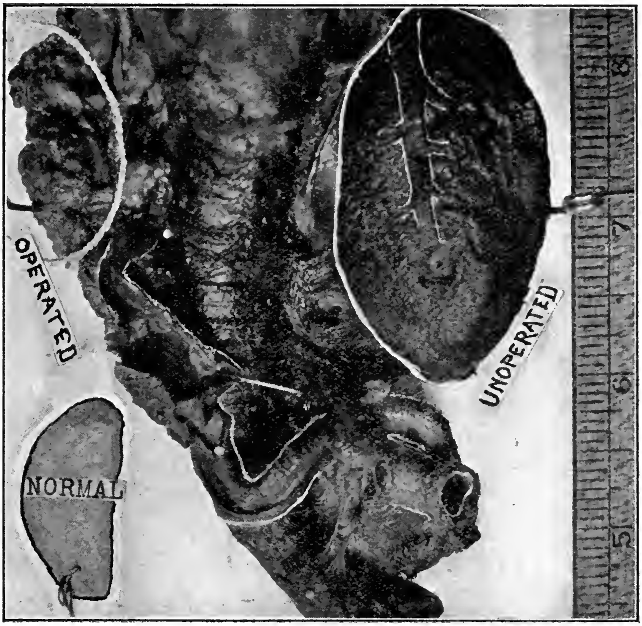


Fig. 90.—Showing the Results of Reversal of the Circulation in the Right Internal Jugular Vein upon the Right Lobe of the Thyroid after Six and One-Half Months.

At the time of operation the thyroid lobes were greatly and symmetrically enlarged. The central end of the left common carotid artery was anastomosed to the peripheral end of the right internal jugular vein, both vessels being ligated and divided for the purpose. Before operation, the dog, in addition to presenting the very large symmetrical goitre, was very fat, and the coat harsh, and much of the hair on the back had been lost. Immediately after the operation the right lobe became greatly enlarged and œdematous, and showed marked systolic expansion. From this stage the gland rapidly diminished in size and became dense to the touch; also, the general symptoms improved and the coat as well. Gland marked "Normal" was taken from a normal dog of the same size for comparison.

the effects of ligation of the veins. A condensed account of the operations and results will best portray the experiments.*

Marked anatomical changes occur in enlarged or goitrous thyroid glands of dogs after alteration of the circulation. The greatest

* A paper with Dr. A. H. Ryan, appearing in the *Interstate Medical Journal*, St. Louis, Mo., February, 1911, is freely drawn upon in the succeeding pages.

changes observed occur when the circulation is reversed in the inferior thyroid vein by anastomosing this vein with the central end of the common carotid artery, or by making the anastomosis of the artery with the peripheral end of the internal jugular vein below the point of origin of the inferior thyroid vein, and ligating the jugular vein distal to the superior thyroid branch. The gross changes consist of a temporary swelling, followed by a marked decrease in size of the lobe on the operated side. The lobe feels much harder and denser. Microscopically, if the goitre be of the hyperplastic type, generally more normal staining colloid is seen after the operation; while, if the goitre be of the colloid type, a decrease in the colloid substance is observed. In both cases the operated lobes in size, physical properties, and histological structure, tend to revert to the normal.

UNOPERATED. OPERATED.

FIG. 91.—MICROPHOTOGRAPH OF THE THYROID LOBE OF A DOG SIX AND ONE-HALF MONTHS AFTER OPERATION.

The right side shows the structure of a bit of the goitrous thyroid tissue from the left (unoperated) lobe. The left side shows the structure of a bit of tissue removed from the right lobe, on which side the circulation was reversed in the internal jugular vein.

The general behaviour and metabolism of an animal subjected to such an operation may undergo striking changes. In Dog No. 16, whose history follows, observations as to condition and studies in metabolism were made both before and after such circulatory alterations in the enlarged thyroid gland. A control dog was observed and studied over the same period, having been subjected to an operation on the same day that Dog No. 16 was operated upon. The operation in the control dog consisted in interposing a preserved segment of vessel between the cut ends of the common carotid artery, this requiring about the same length of time as the thyroid operation. The results are shown in the following table and protocol:

METABOLISM TABLE.

Day of Experiment.	Control Dog.			Dog 16.		
	Food. Gm.	Water. C.C.	Urine. C.C.	Food. Gm.	Water. C.C.	Urine. C.C.
1 (April 24)	114	30	—	204	40	248
2	125	160	262	90	70	122
3	146	175	230	159	359	212
4	156	247	122	171	363	138
5	177	196	219	230	340	234
6	—	112	198	—	350	258
Average	120	153	172	142	254	202
7 (Operated upon both dogs)	—	—	—	—	—	—
8	—	—	—	—	—	—
9	—	—	—	—	—	—
10	158	30	—	169	110	—
11	68	98	94	166	354	—
12	208	35	164	295	328	100
13	200	116	252	272	295	250
14	145	106	—	178	377	290
Average	156	77	102	216	293	128
15	116	185	232	337	295	210
16	112	160	258	83	310	356
17	176	190	98	378	330	176
18	200	145	150	166	700	532
19	150	154	—	150	514	534
20	95	225	132	200	432	420
21	—	110	156	—	460	274
Average	121	167	146	188	434	357
32	40	60	—	123	90	—
33	95	120	—	250	340	214
34	160	155	180	233	450	252
35	216	185	170	175	445	270
36	196	120	215	180	246	178
37	91	30	200	98	290	265
38	—	135	—	—	200	120
Average	114	115	109	151	294	186

The body weights were as follows :

Control Dog.		Operated Dog.	
April 24, 1908	8,620 gms.	April 22, 1908	6,300 gms.
May 5, 1908	8,000 ,,	May 5, 1908	5,750 ,,
May 15, 1908	7,500 ,,	May 15, 1908	6,200 ,,
May 26, 1908	7,550 ,,	May 26, 1908	7,650 ,,
June 1, 1908	7,500 ,,	June 1, 1908	7,300 ,,
		Dec. 1, 1908	8,900 ,,

Note.—The food consisted of cooked hotel meat scraps, gravy, bread, and potatoes.

Protocol I.

REVERSAL OF THE CIRCULATION IN THE THYROID VEINS OF ONE LOBE OF A GOITROUS THYROID, AND LIGATION OF THE ARTERIES TO THE OTHER LOBE.

Dog No. 16: Light yellow adult bitch. Presented large bilaterally symmetrical goitre. Animal very nervous and easily excited, thin

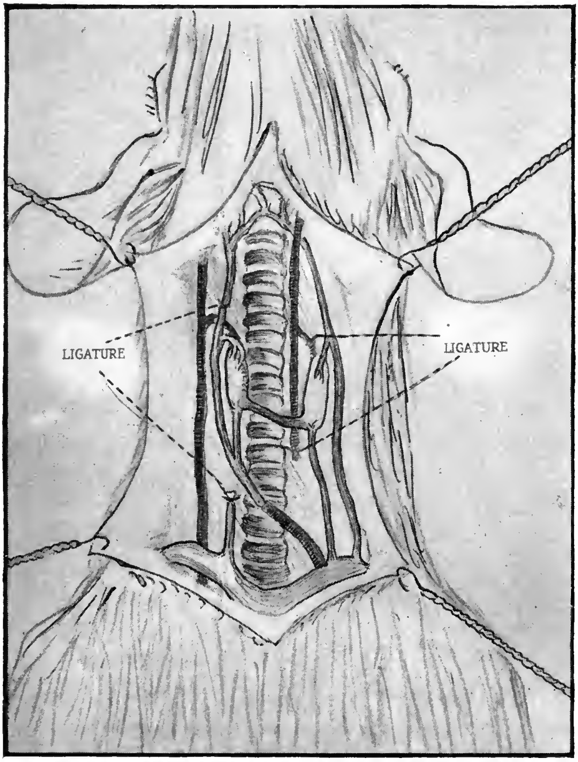


FIG. 92.—DIAGRAM OF OPERATION PERFORMED ON DOG 16.

in flesh, and coat harsh. Eyes very prominent; pulse rapid. Kept in roof kennel with daily access to open roof space for exercise from February 25 to April 24. Little or no change in animal's condition during this period, or, if anything, the general symptoms were more pronounced.

April 24.—Placed animal in metabolism cage. Weight at this time 6·3 kilos.

April 30.—Etherized, shaved neck, and prepared for operation. Opened neck by incision in mid-line from lower level of cricoid cartilage to near manubrium of sternum, and separated tissues down to anterior surface of trachea. Both thyroid lobes about same size; neck enlarged and soft. Exposed and placed temporary clamp on right internal jugular vein below mouth of

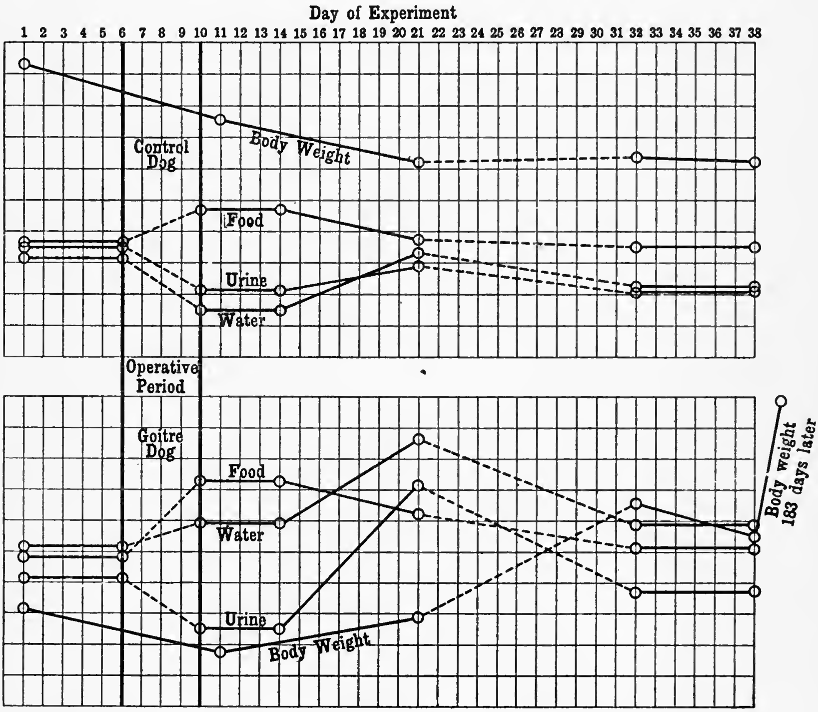


Fig. 93.—Metabolism Chart (Dog 16).

Curves as plotted from averages as shown in metabolism table. Body-weight: two and one-half spaces equal 1 kilo. Food: three spaces equal 100 grams. Water and urine: two spaces equal 100 c.c. Since the chart is constructed from the table, the exact figures are readily obtainable.

inferior thyroid vein. Ligated below this point, and divided between the ligature and clamp, and prepared the peripheral end for anastomosis. Exposed left common carotid artery, and placed temporary clamp below and ligated above, central to the superior thyroid artery. Then divided between the ligature and clamp, and prepared the central end for anastomosis, and united it to the peripheral end of the previously prepared jugular vein by end-to-

end anastomosis. Removed clamps from the newly constructed vessel, thereby reversing the circulation in the peripheral portion of the right internal jugular vein and its branches. Ligated the main trunk of the vein just above the superior thyroid vein; also ligated the left superior thyroid artery, thus decreasing the arterial blood-supply of that lobe. The circulation in the right lobe of the thyroid at this time presented the appearance of enormous activity, the lobe rapidly swelling, the vessels seen on its surface standing out prominently, and the whole mass being of an arterial hue and pulsating strongly. Evidences of œdema rapidly appeared, so that within a few minutes the lobe presented a greatly swollen and œdematous appearance. Closed wound in neck. Swelling of right thyroid lobe still increasing. Applied large soft dressing, and placed animal in hospital. The animal speedily recovered from the anæsthetic, and appeared not to be in pain and but slightly inconvenienced by the operation.

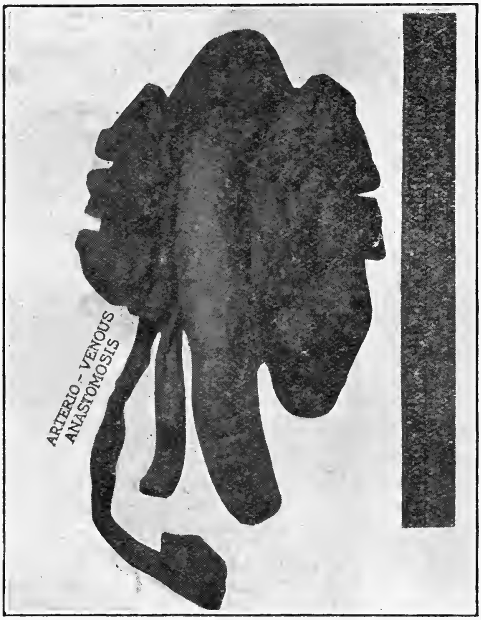


Fig. 94.—Dog 16. April 30, 1908: Anastomosed Peripheral End of Right Internal Jugular Vein to Central End of Left Common Carotid Artery. Tied Left Superior Thyroid Artery. November 30, 1908: Took Specimen.

Shows relative size of the two thyroid lobes. The serrations in the sides of the lobes resulted from the removal of bits of tissue for histological examination.

May 1.—Swelling enormous, but dog happy.

May 4.—Swelling much reduced; bandage very loose; wound dry. Placed animal in metabolism cage; very lively and happy.

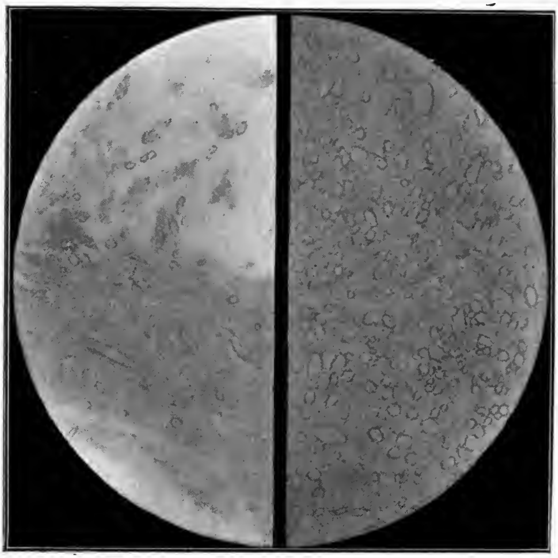
May 9.—Lobe decreased in size; very tense, with strong systolic expansion; left lobe soft.

May 12.—Pulse decreased; right lobe apparently decreasing in size.

May 21.—Operated lobe about one-third size of unoperated, and very dense. Unoperated lobe soft. The animal has been in splendid health and spirits since recovery from the operation—in fact, much less excitable. Nervous symptoms completely disappeared. Hair is being shed very rapidly.

November 30.—Killed by other dogs.

Post-mortem examination revealed very large thymus gland. The operated thyroid lobe measured 5 by 2·5 by 2 centimetres; the



UNOPERATED. OPERATED.

FIG. 95.—MICROPHOTOGRAPH (RETOUCHED) OF THE THYROID LOBE OF DOG NO. 16, SEVEN MONTHS AFTER OPERATION.

The right side shows the structure of a bit of the goitrous thyroid tissue from the left lobe, to which the arteries were tied. The left side shows the structure of a bit of tissue removed from the right lobe, on which side the circulation was reversed in the inferior thyroid vein. Both specimens were taken from the posterior poles of the lobes.

unoperated thyroid lobe measured 8 by 4·5 by 3 centimetres. The right lobe was very dense and markedly bi-lobed, due to transverse constriction, which was a little nearer anterior than posterior pole. Posterior division of right lobe slightly denser than anterior portion. Removed specimen from both divisions, and preserved in 10 per cent. formalin in 0·9 per cent. sodium chloride. Both lobes gave small quantity of clear, viscid fluid on sectioning, but the right lobe

least. Left lobe very soft. Anterior half contained cavities that easily admitted the index-finger, and they were full of bloody fluid. Posterior half much denser than anterior, but *much* more flabby than *operated* lobe. Preserved specimens from both anterior and posterior divisions. All specimens were removed from postero-lateral surfaces of lobe. Posterior end of left lobe contained some clearish fluid.

Removed gross specimen from neck, photographed, and preserved. Weight of dog, 8,900 grammes. Animal in fine condition.

Microscopical results are shown in the figure, from which it is seen that the structure of the right lobe was the more nearly normal.

In a case where one lobe of the thyroid gland was removed and replaced, with reversal of the circulation, extensive changes occurred. After a temporary swelling the operated lobe became smaller and more fibrous. The unoperated lobe presented the appearance of a colloid goitre. New factors are introduced here since there was temporary anæmia, perfusion with sodium chloride solution, and severance of nerves.

Summarized, such results show that when the circulation is reversed in the veins of a thyroid lobe, the ultimate result is a decrease in the size of the lobe. In histological structure it returns toward the normal. When general symptoms are present, these tend to disappear.

Similar results on size and structure appear to follow simple ligation of the thyroid veins of enlarged thyroid lobes, but the changes are of less magnitude.

Protocol II.

LIGATION OF THE VEINS OF ONE LOBE OF A NORMAL THYROID GLAND.

Dog 33 : Black-and-white adult female ; weight, 6 kilos.

January 27.—4.12 p.m. : Operation begun. No difference in size of the thyroid lobes ; gland apparently normal.

4.15 p.m. : Ligated internal jugular vein on the right side below the origin of the inferior thyroid vein.

4.23 p.m. : Operation finished.

January 29.—5 p.m. : The lobe on the right side is enlarged, being the size of a small walnut. The lobe on the left side is smaller than that on the right side.

January 30.—2 p.m. : The gland is the same as when last observed.

January 31.—12 p.m.: No change in gland.

February 2.—2 p.m.: The swelling has disappeared on the right side.

February 3.—1.30 p.m.: The right lobe is slightly larger than originally (apparently), and is rather firm; the left lobe is slightly larger than the right, seemingly slightly larger than before operation, and perhaps a trifle softer.

March 27.—Animal injured in a fight.

March 31.—Animal in excellent condition, except for injuries. Chloroformed, and exposed thyroid gland. The right lobe (operated) is about one-fifth smaller than the left (unoperated).

Protocol III.

Ligation of Thyroid Veins and Superior Thyroid Artery.

Dog 35: White bull-terrier, male.

April 16, 1909.—2.26 p.m.: Operation begun. Both thyroid lobes the same size; the gland appears to be very slightly enlarged.

2.30 p.m.: Tied the main trunk of the inferior thyroid vein below the lobe on the right side; separated the gland from its surrounding tissue.

2.34 p.m.: The blood in the artery on the right side assumed a venous hue. Tied the superior thyroid artery on the left side, which lay alongside of the lobe.

2.36 p.m.: The right lobe is becoming œdematous. Tied main branch of the superior thyroid vein on the right side.

2.38 p.m.: The right lobe is somewhat larger than the left.

2.42 p.m.: Wound closed, and operation completed.

April 18.—2 p.m.: Slight swelling in mid-line under lower jaw.

April 21.—3.30 p.m.: No swelling; dressed wound.

April 24.—Wound dry and healing nicely.

After an operation involving the thyroid veins there is a primary swelling, and this may be followed by a final decrease in the size of the operated lobe of the gland. Gross anatomical changes in a normal gland following reversal of the circulation in the inferior thyroid vein are similar for at least six days after the operation, though less extensive. Great variation in the results occur following ligation of the thyroid veins, which probably is due to the great variation in their anastomotic connections.

Ligation of the superior thyroid artery has not given marked ultimate results (see Protocols I. and III.). In another case the

arterial supply to one lobe of the gland was decreased by anastomosing the peripheral end of one common carotid artery to the central end of the internal jugular vein, the anastomosis being made below the origin of the superior thyroid artery. This decreased the blood flowing through the superior thyroid artery. Five years after the operation the two lobes were compared, and the specimens taken. The gland on the operated side was smaller, being

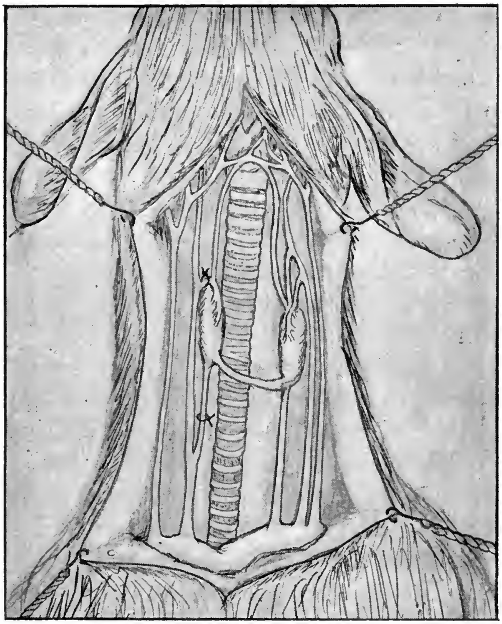


Fig. 96.—Diagrammatic Drawing showing Veins of the Neck of the Dog, with Free Venous Anastomosis of Thyroid Veins, and also the Vessels Ligated at an Operation.

Though the conditions shown were observed several months after ligation of the superior and inferior thyroid veins, only a slight decrease, if any, in the size of this thyroid lobe occurred. The slightness of the change is ascribed to the free venous anastomosis.

1·5 centimetres by 3 centimetres, as compared to 1·5 centimetres by 4·5 centimetres, the size of the unoperated lobe (see p. 95).

In general, after reversal of the circulation in the thyroid veins by arterio-venous anastomosis, or after ligation of the veins of one lobe of a goitrous gland, there has been evinced a tendency of the operated lobe to return towards the normal structurally. Also with this there may occur an alteration in the metabolism of the

animal, while the general behaviour changes toward the normal (the latter being determined by direct observation).

From the above results it is clear that such circulatory changes may result in great alteration in the size and structure of the thyroid gland, and also in the general condition of the animal. The explanation of these results is not a simple matter. Changes in the size and structure of the thyroid gland have been produced by other means, so it is of interest to mention certain of the results and views of other investigators, in that they aid in interpreting the results following alterations in the circulation as above reported.

It is obvious at the outset that if there are common factors concerned in all the various methods of producing changes in the size and structure of the thyroid gland, they are more or less obscure, for such changes can be produced in widely differing ways. Under physiological conditions the thyroid gland may become enlarged, as at puberty or during pregnancy, and it may become decreased in size in old age. Whether these changes are associated with a disproportion between supply and demand of the thyroid secretion is as yet unknown.

Enormous enlargements of the thyroid may occur without any untoward symptoms of a clinical character, while smaller goitres may be associated with the gravest general disturbance. Many attempts have been made to classify these conditions, but as yet none such has been satisfactory from all standpoints. Microscopical structure has been taken as the basis for such a classification. Accordingly, glands of the normal, hyperplastic, and colloid type, with varying combinations of colloidosis and hyperplasia, have been recognized. But when applied to the symptomatic classification, entirely healthy individuals may present colloid glands, and myxœdematous individuals or cretins may present glands of similar microscopical structure. Again, symptoms of a nervous character may be associated with a degree of hyperplasia of the gland not greater than that found in individuals symptomatically normal. Indeed, in a single gland areas of normal, colloidal, or hyperplastic structure have been observed.

Extensive chemical analyses, while seeming to show a relation between percentage composition of iodine and microscopical structure of the gland, have not been shown to bear such relation to the clinical conditions. While in general the symptoms of exophthalmic goitre are associated with a hyperplastic condition of the thyroid gland, and the symptoms of myxœdema are more generally asso-

ciated with anatomical deficiency, their association is not sufficiently constant to establish causal relations between structure and symptoms.

The relation of gland weight to body weight is equally unsatisfactory as a basis of classification. The condition of the thyroid gland as regards size and structure may, therefore, be regarded only as a symptom of the more or less general disturbances called "exophthalmic goitre," "myxœdema," and "cretinism," and not as being pathognomonic.

Perhaps, before reaching such a conclusion, the question of the internal secretion should have been considered in the light of present knowledge of the thyroid gland in its relation to the organism as a whole. Hyper- and hypo-secretion have been ascribed as causes of the conditions called "exophthalmic goitre," "myxœdema," and "cretinism." That the thyroids have internal secretions necessary to the normal activity of the organisms possessing them is concluded from observations too well known to need mention. The universal occurrence of the thyroid structure in all vertebrates, certain of the results reported following extirpation of the thyroid gland—*i.e.*, myxœdema and death—and the improvement of cretinoid individuals with atrophic glandular condition when fed with preparations of the thyroid gland, are ordinarily quoted as indicating such an internal secretion. But from the universal occurrence of this structure it does not follow that this gland is essential to life. For certain other structures are as widespread that are not in this sense essential to life. But that it bears an important relation to the organism is generally admitted. In man, total removal of the thyroid was practised by Swiss surgeons, who record "operative myxœdema" in only a certain number of such cases. With monkeys, Horsley, and Murray and Edmunds have stated that they were able to induce myxœdema; but Vincent was unable to obtain such results. Rats and guinea-pigs, according to Vincent, do not seem to suffer at all from removal of both the thyroid and parathyroid glands; cats and dogs frequently suffer and die, but not invariably; while in foxes death comes on comparatively early. Schiff, in 1856, and later in 1884, reports death following total extirpation of the thyroid gland in dogs. Carlson and Woelfel have removed the thyroids and parathyroids from foxes without fatal results. In one experiment the fox so operated was normal one and a half months after the operation, at which time it was killed. Post-mortem examination

revealed no thyroid or parathyroid tissue, although thirteen suspected glandules were sectioned and examined. In agreement with others, thus far in our own observations on chickens and pigeons total extirpation has not induced a fatal ending. Lanz reports slower development and depressed laying power in a thyroidectomized hen.

In view of such results, the subject presents many difficulties in the way of its solution. While the absence of untoward symptoms following total extirpation is not proof that the gland does not normally functionate beneficially to the animal, it is unwarrantable to conclude that such a function is absolutely indispensable to life.

These considerations are of value when we consider, as previously mentioned, the theories based on thyroid secretion of exophthalmic goitre, myxœdema, and cretinism. The current general conception has been that the symptoms of exophthalmic goitre are due to a hypersecretion of the thyroid gland. This is based on the fact that excessive thyroid administration may produce nervous and circulatory symptoms similar to those of exophthalmic goitre. Removal of portions of the gland, however, has often failed to permanently improve or cure such conditions. Moreover, in addition to the nervous and circulatory disturbances following excessive thyroid administration, metabolic changes are induced.

As opposed to the view of *hyper*secretion are the reported results of improvement of the symptoms of exophthalmic goitre and return of the gland in size toward normal after feeding thyroid gland to such patients.

Returning to the theory of *hypo*secretion as an explanation of the symptoms of exophthalmic goitre, no such symptoms may follow total extirpation of the gland in a patient previously free from these symptoms. Similarly, myxœdema cannot be unqualifiedly ascribed to hyposecretion, for although myxœdema has followed extirpation of the thyroid gland, this is not always the case. No such quantitative theory of secretion will harmonize the evidence presented. And as Carlson and Woelfel have expressed it, "the etiology and symptom complex of exophthalmic goitre in man is too complex for any one theory so far advanced." It should be borne in mind that many of the statements found in the literature were based upon experimental operations performed before the days of aseptic surgery, and that many of those performed at the present day upon animals are done under conditions which would be considered criminal, from a bacteriological and surgical stand-

point, if applied in human surgery. This recalls to mind the variability of surgical results before days of modern methods.

In view of the indefinite state of present knowledge of the activities of the thyroid gland, it is not surprising that little is known of the mechanism of its action, and it would therefore be out of place to enter here into a lengthy discussion of this phase of the subject. But as we are considering conditions which may alter the structure of the thyroid gland, with the hope of correlating such changes with those herein reported following alteration of the circulation, and as the administration of thyroid substance and iodine compounds are reported to induce changes in the gland, some of the results bearing on the question of internal secretion will be presented.

For years before the discovery of iodine certain sea animals and plants containing iodine were used medicinally in cases of goitre. Long ago it was observed that the size of goitrous thyroid glands were sometimes reduced by the administration of preparations of iodine. Similar results were reported following administration of the thyroid gland, as also following administration of iodothyrin. These results led to the view that iodothyrin was the active principle of the internal secretion of the thyroid gland. At present the trend of opinion seems to be that the colloid contains the active internal secretion, and, quoting Marine, "that the physiologic activity of the (colloid) thyreo-globulin is dependent upon the amount of iodine contained in organic combination." The view that iodothyrin was the active principle of the internal secretion was based on results showing the absence of symptoms following thyroidectomy when iodothyrin was administered. Some investigators were unable to confirm these results. But E. Wormser reports that he could prevent the attacks of tetany and preserve the life of an animal for a long time by administering the whole gland. The contradictory nature of the results following thyroidectomy, as previously discussed, render conclusions impossible from the above work. The exact relation of iodine to the activity of the normal gland is not unquestionably established. The question of iodine relation to structure of pathological thyroid glands has been extensively investigated by Marine and Williams, who, in the summary of their results, state that the iodine varies inversely with the degree of hyperplasia. They think that the internal secretory value of the colloid varies directly with its richness in iodine. From this it would seem that the condition of exophthalmic goitre would be

associated with a deficiency of iodine per unit of gland tissue. It is interesting to note, however, that in both colloidal and hyperplastic types of goitre the total iodine or the ratio of iodine to body weight is usually greatly increased, while normal glands have been examined that showed at most only a trace of iodine. But the fact that a gland is poor in iodine and colloid is not proof of deficiency in output—that is, it furnishes little or no evidence of the *rate of secretion*.

As regards the changes in the gland and general symptoms following the administration of thyroid gland or iodine compounds in goitrous conditions, the results by no means indicate that the cause is primarily a change brought about in the nature of the internal secretion of the gland itself. It is true that the iodine content of the gland may increase along with changes in the structure and general symptoms, but to ascribe to the secretions the primary cause of the change would be no more warranted than ascribing the beneficial effects of iodoform on a wound when locally applied, to altered thyroid secretion; for the local application of iodoform in such conditions may increase the iodine content of the thyroid gland.

On the hypothesis that the internal secretion of the thyroid gland was to be found in part at least in the lymph, Carlson and Woelfel made studies upon the lymph of animals, hoping to detect the thyroid secretion. Assuming that the active principle of the internal secretion was the iodine containing compound, they analyzed goitre lymph for iodine, but were unable to detect it. They then made use of the aceto-nitrile test of Hunt, who showed that the resistance of mice to aceto-nitrile was increased by thyroid feeding, while the resistance of rats was lowered. It is desirable to know if the substance or substances in the thyroid gland responsible for the tolerance to aceto-nitrile are identical with the internal secretion. For Hunt has shown that other compounds of iodine may likewise increase the tolerance of mice to aceto-nitrile; also, though to a lesser degree, extracts of other organs give similar results. However, the aceto-nitrile test with mice gave negative results when applied to the goitre lymph by Carlson and Woelfel. Neither iodine nor microscopical structure, according to Woelfel and Carlson, afford an adequate basis for classification of thyroid disturbance in man. For they say, "If the histological structure and iodine content of the thyroid are true indices of the physiological states of the gland, and these are causally, directly, or indirectly

related to the symptoms of cretinism, myxœdema, and exophthalmic goitre, we ought to find these symptoms in goitrous dogs," since the same parallelism exists between structure and iodine content as in man. But such symptoms are rare.

By way of summary, it may be said that we do not know the nature of the internal secretion of the thyroid gland. Furthermore, we are unable to explain the change occurring in the thyroid gland following administrations of thyroid preparations or iodine compounds. And, consequently, we are unable to apply such results to an interpretation of the changes following alteration of the circulation.

There are indications that the relations of the thyroid gland are very broad, so possibly we should not look to the gland alone for an interpretation of the changes produced. Although the thyroid and parathyroid glands are by many considered as distinct, the observations of Vincent and Jolly and others indicate that the parathyroid may be transformed into typical thyroid tissue (as regards structure) after extirpation of the thyroid, and many examples of follicular structure and colloid in the parathyroid glands are cited. The statements that tetany and death result when the parathyroids are removed would seem to speak against the entire assumption of parathyroid function by the thyroid gland after parathyroidectomy. The statements regarding parathyroidectomy are even more confusing than those regarding thyroidectomy alone. Some experimenters have claimed to observe death as a result of parathyroidectomy, while others report the non-occurrence of such results. The problem is even more perplexing because of the minuteness of the quantities of parathyroid tissue which have been reported to have warded off the usual consequences of parathyroid extirpation. To sum up the results of parathyroidectomy, in the hands of some observers tetany and death have ensued in rapid succession after this operation. Other investigators have removed the parathyroids without the invariable occurrence of such symptoms, recovery in certain cases being complete. It has been stated by some of those who have obtained tetany and fatal results as a consequence of parathyroidectomy that such results might be prevented by calcium administration or transplantation of parathyroid tissue. Others have questioned the interpretation of the results obtained after calcium administration in such cases, claiming that the symptoms of tetany were intermittent in character, and that they frequently

stopped in an unaccountable manner, and recovery followed. Of interest in this connection are the observations of Thompson, Leighton, and Swarts, that *operation alone* on the tibia markedly influenced the tetany parathyropriva even after the dog had developed severe symptoms. Leischner prevented tetany in rats by transplantation. But, according to Vincent, the rat rarely if ever shows symptoms after removal of the entire thyroid apparatus, which are attributable to the absence of these tissues.

Halsted, from experiments on dogs, claims such symptoms may be prevented by transplanting one or more of the parathyroids immediately after their removal even into some other part of the body remote from the thyroid. If such autografts subsequently be removed, marked symptoms apparently of the same nature as those produced by simple removal of the bodies ensue. In an extensive series of experiments along these lines, Halsted was unable in any case to successfully graft parathyroid tissue from one animal to another of the same species (isograft). Furthermore, in order to get a parathyroid graft to grow in the animal's own body (autograft), he found it necessary to create a deficiency —that is, to remove most of the other parathyroid material first.

As yet I am unwilling to draw definite conclusions from either of these results, since for the thyroid and other tissues such a law does not hold for certain animals. The writer has obtained results with thyroid, suprarenal, and ovarian tissues, etc., that show that the statement that a deficiency is necessary for a graft to "take" does not hold for fowls. And Magnus's successful exchanging of ovaries between rabbits, and Marshall and Jolly's results on transplanting ovaries in rats, are also against the view. The latter authors conclude that, though more difficult to realize, heteroplastic (isoplastic) transplantations may be successfully performed, especially if the animals are nearly related; also "that the presence of the animal's own ovaries does not seem to exert any inhibitory influence on the successful attachment and growth of additional ovaries obtained from another individual."

Another indication of the broader relations of the thyroid gland is the results of Carlson and Jacobson, who found the ammonia content of the blood to be increased in cats and foxes after complete thyroidectomy, together with depression of the ammonia-destroying power of the liver. Also, the reported hypertrophy of the hypophysis after thyroidectomy, and in many diseases of the thyroid, and the changes observed in it in certain constitutional

conditions; the retarding action of thyroid preparations upon the carbohydrate destroying mechanism of the body; the reduction of the tendency toward ether and adrenalin glycosuria after thyroidectomy; the observations that 86 per cent. of the myxodematous subjects are females; and the reported anomalies in the development of chicks hatched from eggs laid by thyroidectomized hens, indicate that there may be relations of the thyroid which are as yet unsuspected.

From the foregoing it is seen that little is to be obtained from the enormous literature on thyroid which will help in interpreting the results obtained by alteration of the circulation in goitre. An hypothesis ascribing such changes to a primary alteration of the secretion of the gland would be hard to construct on the basis of the facts at hand. The relations of thyroid and parathyroid to each other and to the organism as a whole are, at most, only partially established.

In considering the results following alterations of the circulation from the standpoint of glandular changes following such procedures, it is not implied that the primary glandular changes are initiating causes of the general results observed. While it is possible that the primary changes produced by reversal of the circulation in some of the veins of the thyroid gland (as was done in Dog No. 16, p. 169) are responsible for alterations in the general metabolism and the general improvement observed, such a conclusion is by no means warranted. But to entertain for a moment the hypothesis that it is responsible for the change produced, we might consider that the symptoms of nervousness and metabolic disturbances observed before the operation in this dog were due, say, to a hyposecretion of the thyroid. Not that the thyroid gland was giving off a less amount of internal secretion than normally secreted by the gland, but that there was a state of hyposecretion in the sense that the demands for this secretion were greater than normal. Reversal of the circulation might then be considered as meeting the demands by augmenting the amount of acting thyroid secretion per unit of time, and in this way temporarily correcting the deficiency, the immediate results instituting a permanent beneficial change.

The metabolic changes, and changes observed in the general condition of this dog, are interesting, whatever may be their cause, for a parallelism seemed to exist in this animal between glandular changes and the clinical symptoms which were of the character of

exophthalmic symptoms frequently observed in man, but very rarely in dogs. Other hypotheses could be advanced, but merely one is cited as indicating the possible broad changes which could be conceived as resulting from circulatory alteration.

Turning to the local causes of the structural changes occurring in the gland itself after circulatory alteration, we will consider them from intra- and extra-vascular standpoints. The intravascular changes include such phases as anæmia, hyperæmia, functional activity as related to blood-supply, capillary pressure, rate of flow; and the extravascular changes comprise œdema, tissue respiration, and survival and functional activity under altered extravascular conditions.

The circulatory alterations produced in goitre and described, have brought about, so far as immediate results are concerned, three distinct conditions—namely, partial anæmia alone, as when the artery to a gland is ligated, or when the blood-pressure in the parent artery (carotid) is reduced by anastomosing the peripheral end of this vessel to the central end of the internal jugular vein; partial anæmia with congestion, when the thyroid vein or veins are ligated; and hyperæmia, with reversal of the circulation, when an arterio-venous anastomosis is made with the inferior thyroid vein or parent vessel. Anæmia then occurs in the first two conditions, but not in the last. Partial asphyxiation of the tissue elements, as a consequence of anæmia, is, therefore, an early factor in the production of the noted changes. Asphyxiation is also very probably a factor in the production of the changes noted after arterio-venous anastomoses. But it is probably more largely due in this case to the extravascular changes, such as œdema, which will be discussed presently. Anæmia has been defined from the standpoint of physiological blood-supply, which is considered to be an adequate blood-supply for the functional state of the tissue. The factors concerned are quantity of blood to unit mass of tissue per unit of time and the state of tissue demands (p. 132). While occlusion of the veins would produce a congestion, and in the pathological sense a passive hyperæmia, there would be a partial anæmia in the sense that the arterialized blood-supply per unit of tissue per unit of time would be reduced. Also there might follow an increased tissue demand through asphyxial stimulation (see p. 140).

The exact immediate conditions produced in the tissues by such procedure as ligation of vessels or the effects of rapid severe œdema

are little understood. While the degree of anæmia produced would, on the whole, vary directly with the degree of circulatory obstruction, transient conditions might occur in the smaller vessels producing varying anæmic and asphyxial states not indicated by the primary circulatory obstruction. For example, the partial anæmia induced by the vascular ligation might, by the stimulating action of asphyxia upon the arterioles, and even the capillaries, cause a greater degree of anæmia by the contraction of these vessels. This would introduce the question of the relative resistance of tissue elements to the adverse conditions of asphxyia, as also the ultimate survival of tissues, under the varying degrees of anæmia that might be produced. But this is considered below.

In considering the results following simple ligations of the superior thyroid artery (as was done on Dog No. 16, p. 169), from the standpoint of anæmia, it is first necessary to know the relation of blood-supply to demand. Since partial asphyxia has been used to explain the results following circulatory alterations, and since partial anæmia might be inferred to have occurred in the left lobe of the gland of Dog No. 16, as a result of ligation of the superior thyroid artery, the question arises why no such diminution of the size and change in character of structure occurred in this lobe, as has occurred following ligation of the thyroid veins. A notorious fact is that the blood-supply to goitrous thyroid glands is greatly increased; but as the minimum quantity of blood-supply, which would suffice to maintain a continued state of the goitrous activity is not known, the degree to which the blood-supply could be diminished without producing glandular changes is not known. So, when the artery is ligated, it is impossible to say whether a partial anæmia is produced, for we are ignorant of one of the factors. Where the vein or veins are ligated, the condition is not the same, for the factor of œdema, and its dependent results, is introduced. Furthermore, the ligation of the superior thyroid artery may not have produced a sufficient degree of asphyxiation to lead to the production of a sufficient quantity of disintegrative products necessary to induce the inflammatory changes accountable for the glandular reaction, as elsewhere discussed (p. 189); or, in the absence of œdema (present when the veins are ligated), such disintegrative products, if formed, may be too rapidly removed to bring about this inflammatory reaction, neither the lymphatic nor venous channels being interfered with.

The condition of partial anæmia may be further augmented by

the partial occlusion of the capillaries as a result of increased intra- or extra-glandular pressure produced by the œdematous condition. The factor of anæmia is probably of importance in the extravascular processes which it inaugurates either directly, producing anæmia of the tissue cells, or indirectly, through injury to the vessels themselves, rendering them more permeable, and thereby augmenting the onset of the œdematous state, the effect of œdema being the same as that produced by anæmia—*i.e.*, asphyxia.

In a goitrous gland already hyperplastic the beneficial results to be derived from the production of an active hyperæmia might be doubted. Based upon the results obtained by severing the vasomotor nerves to a part, and thus increasing its blood-supply, it might be anticipated that the production of an active hyperæmia would give rise to a further hyperplasia. But it is easy thus to fall into error. For example,* if the vasomotor nerves to a part be cut, the vascular channels will dilate, and a greater quantity of blood will flow through the part. Greater growth has been observed under such conditions. But although the existence of specific trophic nerve influences is doubtful, if not disproved, it is still possible to object to these results as being due directly to the increased circulation, as it might be due to some change set up in the tissues themselves by cutting the nerves; for when such nerves are sectioned, fibres other than vasomotor fibres are severed.

Assuming that no such nervous trophic influences are concerned in the phenomena, it by no means follows that the result is due to a better nutrition of the part from the presence of a greater circulation—that is, one cannot conclude that the growth of a tissue may be augmented by merely supplying it more abundantly with blood, for in meeting conditions necessary to accomplish this an abnormal state of the capillary circulation is inevitable, and it is possible that this in itself, acting either directly, as by pressure upon the tissue elements, or indirectly, through changes taking place within the capillaries themselves, resulting in an alteration of the normal function, might result in stimulating the tissues to greater activity. For example, such an hyperæmic state is usually, if not always, accompanied by an increased pressure within the capillaries. This condition might favour the passage of substances used by the tissues out of the blood more than it would favour the entrance into the blood of waste products from the tissues. Thus

* The following page or two are taken from the chapter on Anæmia and Hyperæmia, but in order to avoid interruption repetition is made.

the accumulation of waste products might serve as a stimulus to the tissues, and an abundance of food materials being supplied at the same time, it is conceivable that hypertrophy might result.

Again, it might be urged that, owing to the greater amount of blood flowing through the part, the temperature of the part would be increased; and owing to the increase in temperature, the tissues might manifest a greater activity. That this last view may be the key to the explanation is indicated by the fact that some of the best observations of this character have been made upon external structures, such as rabbits' ears and cocks' combs, where the actual increase in temperature may be considerable. For if such an experiment be performed upon the ear of a rabbit, a very marked difference in the temperature of the two ears will be observed even by feeling with the hand (*cf.* p. 155).

But reversal of the circulation in the veins of the thyroid gland does more than increase the flow of the blood. So, while hyperæmia is a factor in the production of the end results, it probably acts indirectly.

When the central end of an artery is anastomosed to the peripheral end of a vein, the result is that in the venous portion of the vessel the direction of the circulation is the reverse of the normal, the pressure is higher, and the blood is arterial. The pressure in the capillary area normally drained by the vein will be increased, for not only has the vein ceased to transport venous blood away from the capillaries, but it has engaged in conveying arterial blood to them. So the capillary pressure is raised not only by the damming back of the blood by the vein having ceased to convey venous blood (passive anæmia), but, by the vein leading more blood into the part, the pressure in the capillaries is further augmented. Some of the blood sent back to the heart through the veins no doubt may reach unobstructed venous trunks through direct anastomotic connections, and these quickly respond to the new conditions, and rapidly enlarge to accommodate more blood in passing to unobstructed veins returning to the heart. So the greatest increase in capillary pressure due to the reversal of the direction of the circulation in the vein would be observed shortly after the operation. And experimental observation bears this out, for when the central end of one common carotid artery is anastomosed with the peripheral end of the inferior thyroid vein on the opposite side of the neck, the effect upon the circulation in the gland is immediate and striking. This is observed particularly if the

gland present the condition of well-marked goitre—that is, if it be markedly enlarged and the blood-vessels prominent. On occluding the vein preparatory to division and anastomosis with the artery, the gland may swell somewhat and become purplish—that is, present the appearance of passive anæmia or engorgement with venous blood. But very quickly after the new circulation is established it not only becomes greatly enlarged in size, and the blood-vessels become more engorged, but very red or arterial in hue. The possible increased rate of flow through the capillaries may interfere with the metabolism of the cells which derive their nutrition directly from the blood-stream—*i.e.*, the intimal cells of the blood-vessels—or the increased capillary pressure may in some way interfere with the normal metabolism of the capillary endothelium, or may mechanically injure this structure. At any rate, evidence is shown that the normal properties of the capillaries are affected, by the passage of liquid from the blood through their walls into the surrounding tissues, producing the phenomena of œdema.

As to the interpretation of the changes which affect the extravascular tissues, they are in part explainable from the changes within and affecting the blood-vessels, and also in part to the extravascular conditions established as a result of the circulatory derangements. It is impossible with our present knowledge to enumerate in detail all the factors involved, but it is, nevertheless, interesting to consider certain factors which undoubtedly play rôles in the production of the extravascular phenomena. Thus, as a result of the increased capillary pressure, the tissues become œdematous—that is, they become infiltrated with liquid, the flow of this liquid being chiefly in one direction—namely, to the tissues. The conditions for return of tissue metabolic products are unfavourable. This would lead to an abnormal concentration of such substances in the tissues. Since it is known that the functional activities of tissues are harmfully affected even to the point of extinction of vitality in this way, we have a theoretical explanation for the interpretation of the changes observed. Also the same condition results in an increase in the extravascular pressure upon the tissues, and this, too, in all likelihood may affect the activities of the tissues in the same direction. Reducing the interpretation to terms of respiration in order to simplify the conception, these conditions would result in an asphyxial state in the tissues. And in line with what is known regarding the relative susceptibility and

resistance of tissues to such an adverse condition, we have a rational explanation of the tendency of the tissue elements to later present more normal morphological characteristics — that is, it seems probable that the abnormal tissue elements are less resistant to the adverse condition than are those which are more nearly normal. Therefore, the more nearly normal elements would, from this standpoint, be expected to better survive the adverse condition (p. 139).

Bearing directly upon this point is a consideration of the nature of the abnormal tissue elements; for if it is assumed that the abnormality is developed in cells arising primarily as normal thyroid tissue elements, and this seems the most rational conception, then it would seem that the more nearly normal cells of the thyroid tissue would be the youngest. Now, since it is well known that in general the ability of a tissue element to withstand or survive an adverse condition is in inverse proportion to its age, it follows that cells of the thyroid surviving such treatment would be of the younger type. This view harmonizes with what is said in the preceding paragraph.

Another consideration is the possibility of a greater susceptibility of abnormal elements to the action of substances of the liquid extravasated from the blood-vessels. But since nothing definite is known upon this point, and since its interpretation would in the broad sense be from the standpoint of interference with the respiration of the tissue elements, it is unnecessary to consider it further.

Another possible factor would be in connection with the possible and even probable stimulating action upon the tissue activities, thus causing an increase in the production of internal secretion. But since the question as to whether the general symptoms are due to a hypo- or hyper-secretion, or to some condition outside the thyroid apparatus, is so unsatisfactorily answered, it would be unprofitable to go into the matter.

The final results as regards the ultimate glandular changes, on the whole, depend upon the extent of the initial circulatory alteration. As shown in the figure (p. 175), after ligation of the inferior and the superior thyroid vein there was at most a very slight decrease in the size of the operated lobe. This figure, illustrating the venous supply of the thyroid gland in this animal, shows that the operated superior thyroid vein had a very large anastomotic connection distal to the ligature, and also that the thyroid lobes were connected by an isthmus. Both of these structures would render collateral

circulation possible, which would tend to prevent the establishment of the desired initial circulatory change.

Generally speaking, the results obtained from ligation of the veins depends upon the extent of primary venous obstruction. This in turn affects the tissues concerned in a way similar to the action of asphyxia in other tissue, the results "depending upon the given state of metabolism when the nutritional change is made, and the extent of the nutritional change in the given condition," as discussed elsewhere in considering the relation of asphyxia to the central nervous system (Ryan and Guthrie).

It may be said that the changes observed in goitre following circulatory alterations may be rationally interpreted from the standpoint of primary interference with the respiration of the tissues, probably resulting in the death and disintegration, and in the disappearance of abnormal tissue constituents. Also, accompanying the secondary effects due to the reactions of the tissues, absorption is probably increased, so that the abnormal substances are quickly removed from the gland, which accounts for their rapid disappearance. The more nearly normal tissue elements, being more resistant, or perhaps more favourably situated to survive, under the more nearly normal circulatory conditions established through the reaction of the tissues to the adverse condition—which, indeed, is strikingly similar to the current conceptions of an inflammatory reaction—resume and retain more nearly normal functions.

As to the reaction set up in the tissues, it is explainable as being due to the œdema. But this in truth may be only the indirect cause, for the accumulation of metabolic products, together with substances originating from the death of tissue elements, would probably act, either together or the latter alone, more directly in producing an inflammatory reaction.

On the whole, the results indicate that general symptoms of goitre are at least in part associated with deranged functions of the thyroid apparatus. The evidence may perhaps be considered as more conclusive from clinical observations, for it is well established that amelioration, or even disappearance, of general symptoms may in certain cases follow surgical operations. Also, such results are known to follow local treatment of pathological thyroids, such as an injection of carbolic acid. Similarly, the results reported following ligation of the thyroid arteries, and more recently, as herein stated, the amelioration or disappearance of general symptoms following ligation of the veins, or division of the ligated vein distal to the

ligature, and anastomosis of its peripheral end to an artery, so that the vein transmits arterial blood to the gland, point in the same direction. My results from the operation of tying the veins were studied by Professor Herman Tuholske, after which he performed an operation upon a human patient with good results. Following the publication of this work, Werelius repeated the operation, with the modification that he tied the vessels by means of purse-string sutures introduced beneath the capsule of the gland, and confirmed our results, particularly as to the decrease in size of such operated glands, together with changes in structure. He also operated upon a human being in the same manner, from which he reported good results.

From our results, though cases presenting marked general symptoms are not numerous, which is in agreement with the statement made that the occurrence of such general objective symptoms in goitrous dogs is comparatively rare, the evidence speaks for the occurrence of such symptoms as being due—at least, in part—to the deranged thyroid ; for such animals as have presented general symptoms have always shown an amelioration or disappearance of such symptoms following operations upon the thyroid veins. But it must be remembered that operative procedures in general, themselves may lead to such results in this as in other pathological conditions. The explanation of these results therefore remains obscure.

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CHAPTER VIII

TRANSPLANTATION OF TISSUES

Introduction.

Transplantation of protoplasm is of the widest occurrence in Nature. The very existence of the higher plants and animals is proof of this, for it is through transplantation of protoplasm—fertilization, as it is called—that such organisms originate. In plants the male element or pollen is carried to the ova. Gravity or air-currents are the most important directing carrying agents in some instances, as in Indian corn or maize, while insects play important rôles as transmitters in others. Turning to animals, the circumstances and the *modus operandi* vary widely. For example, in frogs the ova are deposited outside the body, along with an abundant supply of food material, and the sperm or male elements are deposited on the eggs outside of the body. Thus, both the maternal and paternal elements are transplanted. In the case of mammals the parental elements are united inside the body; but the ova are transplanted from the ovary to the uterus, and the sperm from the testicle into the ova. Such is the natural process. The resulting organisms may or may not present identical objective characters to those of the parents.

By artificial means it is possible to remove the fertilized ova of a mammal and to successfully grow them by placing them in the uterus of another animal.

Another form of transplantation is observed in the propagation of plants by cuttings. Thus, a geranium plant or a grape-vine may result from the introduction of a severed leaf-stalk or stem into suitable soil under proper conditions of temperature, moisture, and light. Such plants may present all of the characteristics of the original, and this is not surprising, for the plants are not new individuals, but merely extensions of the plants from which the cuttings were taken.

Another very common form of transplantation is that practised by horticulturists in the propagation of plants, such as fruit-trees. This consists of exposing and bringing into contact the inner tissues of two plants. A bud or small twig is commonly engrafted on to the trunk or root of another individual. The growth resulting from the graft commonly present the same objective characters as the individual supplying the bud or scion.

In the case of the higher animals, in many respects a surprisingly great parallelism to what has just been stated for plants is observed. But certain wide differences exist. For example, although a tissue may be successfully engrafted, such grafts do not show any evidences of endeavouring to grow directly into a complete organism, as in the case of a length of grape-stalk set in the earth (unless autochthonous teratomata be an instance). Tumours, particularly those that form metastases, as carcinomata and sarcomata, illustrate a common natural form of transplantation in animals—that is to say, tissue elements, when deposited in new parts of the body, may grow. This happens most commonly in the case of tumours that have a tendency to break up or to give off fragments. Such fragments may be launched into the lymph- or blood-streams, and thus transported to and lodged in remote regions of the body. The new growth usually presents the same objective characters as the original tissue, but this is not always the case. But in mammals the deviation from the original tissue is relatively slight. Certain tissues, however, appear to be able to take on the characters of different kinds of tissues. This phenomenon is spoken of as metaplasia. In general, the process is morphologically limited to the acquisition of characters of a different variety of the same class of tissue. It may occur in certain tissues of either ecto-, meso-, or ento-dermal origin. But certain tissues of each group more rarely or never arise in this way; nor may a tissue of one class arise from a tissue of another. Thus, sudoriferous glandular epithelium may be transformed into cuticular epithelium, but not into a nerve cell; connective tissue may become transformed into cartilage or bone, but not into muscle; and parathyroid into thyroid, but not into kidney or liver.

Artificially, the widest variety of transplantations may be successfully carried out. For example, small fragments of many different kinds of tissues may be removed and transplanted into remote portions of the body. They may be engrafted into the same animal, or into another closely related animal. Under such circumstances

not only may preservation of structure and growth be observed, but function may be resumed. This is shown by classical experiments upon the thyroid, which, briefly, consisted in establishing—first, that the removal of the entire apparatus was followed by death; second, that if prior to the removal of the organ a portion of it was engrafted into another situation, upon removal of the remaining thyroid tissue death did not occur; and third, if the engrafted tissue was now removed, death promptly took place (*cf.* p. 177).

By this simple method of engrafting tissues only small masses could be successfully employed, for since all vascular connections were destroyed, the survival of only thin sheets of tissue was possible, owing to the abnormal nutritional conditions — that is, normally such a tissue is nourished by circulation of blood through its capillaries. After such an operation, the nutritional commerce is carried out for a time with the liquids surrounding it—that is, outside of it. For obvious physical reasons such an abnormal nutritional commerce can only adequately be sustained with the more superficial cells. For certain purposes only, therefore, is the simple method of transplantation satisfactory, and many tissues cannot be thus transplanted with any hope of functional results. For example, the method is not applicable to tissues highly susceptible to the deleterious influence of temporary anæmia and other unavoidable operative conditions. And, again, tissues of organs normally provided with external channels for the carrying off of secretory or excretory products cannot be expected to long survive such treatment, as no adequate provision can be made for removing the products of their activity. It may be stated that in general such transplantations are best adapted in adult mammals for connective and surface epithelial tissues, and tissues of the ductless glandular type. But it must not be concluded that such transplantations are of little value, for such is not the case. Indeed, many laws governing the successful transplantation of tissues have been worked out by means of such studies; and the method is so exceedingly simple that it may be successfully carried out under conditions which would be entirely inadequate for the more complicated method presently to be described. And for certain types of animals, and under certain conditions, which will be described later (p. 270), the method is entirely satisfactory where it would be impossible, or at least difficult, to employ the more elaborate method involving vascular anastomoses. I refer particularly to the transplantation of the ovaries and testicles in fowls, but the statements

are equally true in many other cases, especially in young animals of small size. But by this method it is impossible to successfully transplant large organs or tissue masses of adult animals of the higher order, or the more delicate types of tissues, owing to the obstacles mentioned elsewhere. So, in order to accomplish this, recourse is had to vascular anastomoses between suitable vessels of the host and the transplanted tissue masses. By such a technique, although it is frankly confessed at the outset that the results actually achieved and reported up to the present writing are by no means so complete or satisfactory as might be anticipated, considering the relatively enormous activity in this particular direction during the past five years, it is reasonable to hope for, and even confidently expect, results of great moment from both the experimental and practical standpoints, for by this method it seems probable that permanent combinations of animal tissues, ranging from parabiosis to the engrafting of the smallest structures of the adult body isolated from other tissues, will ultimately be accomplished. And by this method not only will many strictly physiological phenomena be elucidated, but much light, no doubt, be shed upon a host of other biological problems, such as phenomena of organ inter-relationships, adolescence, senescence, inheritance, and so forth, and definite laws, applicable to surgery, be discovered (*cf.* p. 16).

The methods now to be described are based upon the writer's theoretical conceptions, his experiments and results, and the results of others.

Certain general considerations that are discussed elsewhere are applicable to transplantations with blood-vessel anastomoses. Of these, temporary anæmia, mutilation, care during operation, temperature, and time required, are among the more important, and they are fulfilled to an optimum degree by making the adverse conditions, such as anæmia, as short, and maintaining the temperature at as near the normal degree as possible; and avoiding undue mutilation and handling. The transplantation of a tissue mass distinctly differentiated and marked off from the surrounding tissues by a limiting membrane or capsule, and equipped with a single main artery and vein of fair length, affords the easiest example for transplantation. As these conditions are fairly represented in the kidney, the operation for the transplantation of that organ will be first described.

Transplantation of Kidney.

Two animals, such as dogs, of suitable sizes are prepared, as previously described, for operation (p. 35). As all abdominal transplantations are best performed on the female, owing to the lesser risk of infection through contamination of dressings by urine, a bitch should be selected for the host. One animal is to supply a kidney, and the other to receive it. The bellies of both are shaved from the ensiform cartilage to the pubes, and well around on either side to include the flanks and sides to the lumbar muscles. Both animals should be operated upon at the same time. The operating-table described will serve for two cats or small dogs at one time, the heads being placed at either end.

But it is, perhaps, more convenient to have separate tables. The animals are fastened on their backs, the anterior limbs being drawn forward and the posterior limbs backward. The back of each is elevated by placing a sand-bag or other pillow crosswise beneath it at the level of the kidneys. The abdomen is opened either by a longitudinal incision in the linea alba, or by a transverse incision at the level of the posterior poles of the kidneys or thereabouts. But the longitudinal incision is preferred, as the transverse incision is much more mutilating. The incision is first carried through the skin; the margins of the operating cloths and skin are then fastened together, as in the operation described for the neck (p. 41). The remaining structures of the abdominal wall are severed and fastened to the operating cloths with forceps. If the right kidney is to be operated upon, a soft, dry, lint-free towel, folded once in the middle so as to bring the ends together, is placed on the left side of the wound with the ends outward. The edge formed by folding is then fastened to the edge of the wound by clamps placed at either end. The intestines are then raised from the abdominal cavity, and placed upon the towel. The outer ends of the towel are then folded back over the intestines, and made to snugly inclose them by folding in the sides. Over this is then placed another similar towel. No salt solution or liquid of any kind is employed on the intestines. All unnecessary handling of the intestines is avoided, but they are kept thoroughly protected by towels from undue drying or chilling by the air.

The right kidney is then exposed, excepting for the peritoneum. This is divided at the left of the renal vessels from the mid-line to slightly beyond the outer margin of the kidney. It is carefully

separated from the kidney and renal vessels by passing an instrument, such as a pair of scissors, beneath it, and by opening the blades after inserting them for some distance between the tissues, or by using them as a probe to loosen the peritoneum. The main precaution to observe in this is to make a clean wound in the peritoneum, and to avoid tearing it, so that it may be most perfectly repaired with the least trouble, if it is so desired. The capsule of the kidney is then carefully freed from the surrounding tissues, and the ureter and the mass of accompanying tissue is freed downward from the kidney for several centimetres.

Up to this point the technique has been the same for both animals,

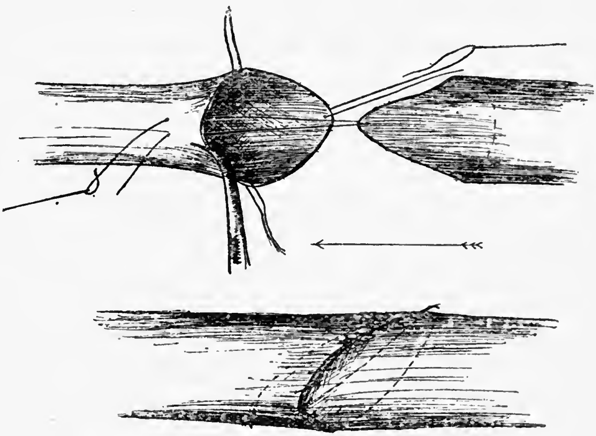


Fig. 97.—Showing Method of Union of Divided Ureters by Invagination and Continuous Suture.

The stitches placed between the fixing sutures need not penetrate the inner surface.

but the levels at which the ureters are clamped and severed is not identical in both. In the animal intended for the recipient, host, or donnée, the mass of ureteral tissue is temporarily clamped several centimetres below the kidney, and section is made near the pelvis of the organ, while in the animal supplying the kidney for engrafting the temporary ureteral clamp is placed near the kidney, and section is made lower down. The reason for this is to preserve a sufficient length of ureter for anastomosing.

The blood-vessels next receive attention. On the host the renal artery and vein are clamped near their mouths, and are sectioned toward the kidney. If it happens that branches are present, they

are temporarily or permanently occluded. In the case of the donor the renal vein and artery are temporarily clamped in the order given, or together near the kidney, and permanently ligated near their mouths.

The renal artery and vein, together with the slender mass of tissues accompanying them, are severed close to the last point of occlusion, and the peripheral ends of the vessels prepared for suture, as previously described (p. 43). The ends of the artery of the host to be used for anastomosis having been prepared, together with a bed for the kidney, the latter is removed from its original position and immediately placed in its new bed. The ends of the blood-vessels are then quickly adjusted and united, and the circula-

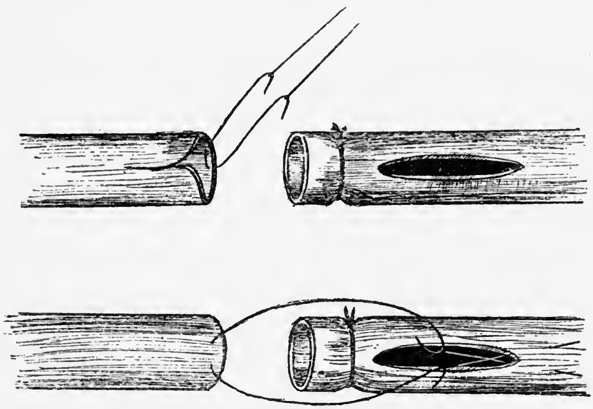


FIG. 98.—VAN HOOK'S METHOD OF URETERAL ANASTOMOSIS.

tion re-established. The ureter is then released from the clamp, and directly anastomosed by continuous stitches, as in blood-vessel anastomosis, to the peripheral end of the divided ureter of the host; or Van Hook's method may be employed. The kidney is then fastened in place by one or more suitable fixing sutures to surrounding tissues, as the lumbar muscles. The edges of the peritoneum are then drawn together and sewed with fine threads, thus closing the wound in the peritoneum and partitioning off the kidney from the abdominal cavity, as is the case normally. The abdominal wound is then closed and the operation is finished. A dressing is then applied, and the animal placed in the hospital.

The method of direct anastomosis is not feasible for very small animals, owing to the small size of the blood-vessels and ureters; and even with large animals it cannot always be followed, for the

reason that not infrequently kidneys are not supplied by single arteries, but by several; so direct anastomosis may not be feasible for this reason. In such instances the kidney may receive several arteries springing from the aorta; or a single vessel may leave the aorta, but rapidly break up into branches.

To meet these conditions the patching method of vascular anastomosis (p. 77) may be employed, especially in the case of a branching vessel, or when there are several independent vessels arising close together so that they are included in a moderate area.

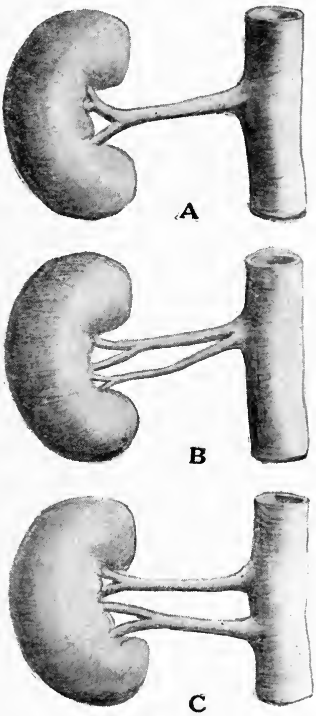


Fig. 99.—Types of Abnormal Renal Artery Distribution observed (cf. p. 232).

But a more satisfactory method in certain cases is to remove segments of the parent vessels, bearing the renal vessels—*i.e.*, the aorta and vena cava—and to interpose them between the ends of corresponding vessels of the host, which have been temporarily occluded above and below and divided, or a segment removed at the point where it is desired to interpose the other segment. The most favourable point for this is slightly posterior to the renal vessel, owing to relative absence of other important branches in this region. It is usually best to ligate and divide one or two pairs of lumbar vessels to give sufficiently long vascular segments to work with. This permits the placing of the temporary hæmostatic clamps at some distance from the ends of the vessels so that they will not be in the way of making the anastomoses. And if the ends of the vessels can be lifted up, the operation will be much easier; but it is possible only temporarily to occlude such branches on large animals. Occlusion of such vessels between the point where the major vessels are temporarily occluded and where they are divided is necessary to prevent hæmorrhage, due to their anastomotic connections.

In the preparation of the vascular segments to be transplanted, all

branches, other than those through which it is desired to re-establish a circulation, including branches from the renal vessels themselves, such as the adrenals, are ligated near their origin, and divided peripheral to the ligatures. Fine silk ligatures are used for all such purposes. Ordinary sewing silk (No. A, white) is almost exclusively employed by the writer. The renal vessels are temporarily clamped, close to the aorta and vena cava, before removing the segments, thus leaving their distal portions and the capillaries of the kidneys filled with blood. The segments themselves are removed and freed from blood, and treated as has been described for the transplanta-

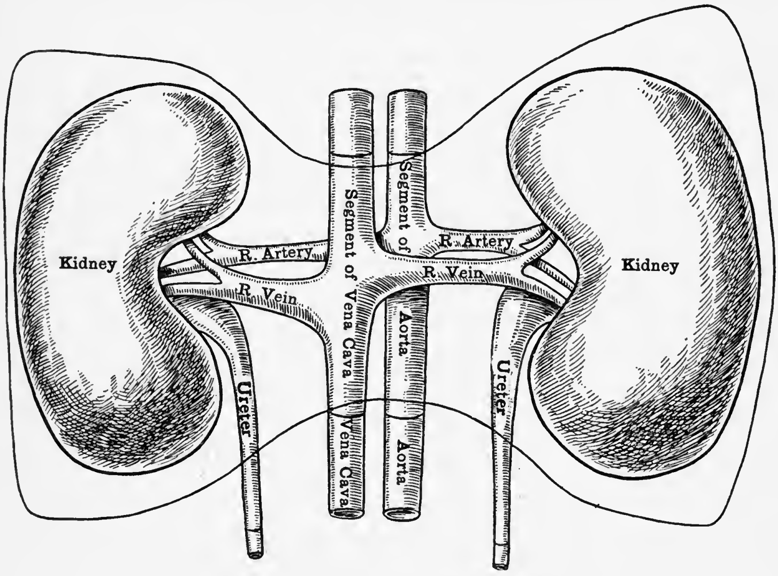


Fig. 100.—Kidneys engrafted in Mass.

tion of a segment of blood-vessel (p. 43). By this method of transplantation it is almost as easy to transplant both kidneys, together with the suprarenal capsules, nerves, and all other attached tissues, as it is to transplant one kidney. The method has been termed "transplantation in mass." A rectangular area of peritoneum lying over the mass that is to be removed and transplanted is cleanly cut out and left adherent to the ventral surface of the tissues. The edges around the lines of division are pushed back sufficiently to permit the necessary operative procedures upon the underlying structures. In preparing the host, the operation is very nearly the same, only a somewhat smaller area of peritoneum is removed; the

ureters are divided somewhat closer to the kidneys, and the renal vessels are ligated and divided between the ligatures and the kidneys. It is well to ligate the renal vessels near the kidneys in order to preserve the circulation through any important branches given off from them, such as the adrenals. If segments are removed from the aorta and vena cava, they are cut shorter than those to be transplanted; but it is perhaps better to cut the segments for transplantation relatively short, making the incisions, say ½ centimetre away from the renal vessels on either side, and to merely divide the vessels of the host in preparation for the segment to be transplanted. All such incisions should be made with the view of avoiding cutting through the mouths of any branches, as such an error may lead to difficulties in making the anastomosis.

In preparing the vessels of the host care is exercised to avoid injury to the large lymphatic vessels; but if such injury be made, no serious results will necessarily follow, as the thoracic duct has frequently been torn in this region without leading to any post-operative symptoms whatever, and human surgical experience supports this view. Many cases of "spontaneous" closure of ruptures of the thoracic duct have been observed.

The ends of the ureters are anastomosed, the kidneys are fixed in place, and the edges of the engrafted sheet of peritoneum and the edges of the host's peritoneum are smoothly stitched together. Other features of the technique of such a transplantation are so nearly identical with that which has been described that a further specific account is unnecessary.

In providing an outlet for such engrafted kidneys, the methods of ureteral anastomosis described are employed, or the whole length of one or both ureters may be removed, together with a portion of the bladder wall surrounding the ureteral orifices, and the whole apparatus transplanted, the patch of bladder wall being sutured into a suitable opening cut in the wall of the bladder of the host.

In the case of a kidney engrafted into another region of the body, as into the carotid triangle of the neck, the ureter has been made to open upon some foreign surface, such as the skin, or into the œsophagus; but perhaps it would be better to anastomose its end to a vein, for thus the risk of infection would be lessened.

Transplantation of Suprarenals.

The suprarenals may be transplanted along with the kidneys in mass, according to the technique described for that operation. The entire arterial blood-supply may be preserved by making the anterior section of the aorta above the mouths of the suprarenal arteries; but even if this is not done a considerable blood-supply to the capillaries is preserved owing to the branches from the renal arteries. But there are considerable variations in the number and size of such vessels, so the adequacy of the circulation by way of renal branches from vessels varies considerably. The bodies themselves could be engrafted by vascular anastomoses without including the kidneys, in which case it would be advisable to ligate and divide the renal vessels distal to the suprarenal branches. The vessels themselves are too small on ordinary laboratory animals for direct anastomosis.

Transplantation of Thyroid.

The technique of thyroid transplantation with vascular anastomoses is carried out by exposing and removing a lobe of the gland, together with the preparation of suitable arteries and veins for anastomosis to vessels adjacent to the situation chosen for its reception. As the blood-vessels of the thyroid are more numerous than those of the kidney, and as they are subject to considerable variation in their relationships and connections normally, an exhaustive account of the possible procedures applicable in transplantation will not be undertaken; but two methods, the one dealing with direct anastomoses of the superior thyroid artery and vein to suitable arteries and veins, and the other a modified transplantation in mass operation, will be described.

In the first instance the superior thyroid artery and vein are dissected out and prepared for temporary occlusion and division. All other vessels entering or leaving the lobe are then ligated near the gland, and cut peripherally to the ligatures. The capsule of the lobe is entirely freed from surrounding tissues, and the isthmus divided. The superior vessels are temporarily clamped near the capsule, and divided near their mouths. The ends are then prepared for anastomosis in the usual manner, and the mass of tissue placed in the new situation previously prepared for its reception. The artery and vein are then united to the vessels prepared for the purpose, and the circulation re-established. The anastomoses may

be of the end-to-end variety, or the ends of the thyroid vessels may be connected with lateral openings in suitable vessels, such as the common carotid artery and the internal or external jugular vein (p. 76). The lobe of thyroid tissue is fixed in place by a suitable fixing suture, and the wound closed.

To carry out the other method mentioned, the common carotid artery and internal jugular vein are ligated above the mouths of the superior thyroid artery and vein. The first-named vessels are divided above the ligatures and temporarily occluded, and again at a point below the major thyroid branches. The vessels, together with the thyroid lobe, are then removed and engrafted, the vessels being united with other suitable vessels, as described for the superior thyroid artery and vein. The advantage of this method is that not only is more complete preservation of vascular connections possible, but much smaller thyroid lobes may be thus engrafted with vascular anastomoses ; for in cases where the thyroid vessels themselves are too small to be directly anastomosed, the parent vessels—*i.e.*, the common carotid artery and internal jugular vein—may be sufficiently large to render successful vascular suture possible.

It is possible to engraft a thyroid lobe of one animal into another animal without interrupting the circulation. The procedure for accomplishing this is as follows :*

The two animals being etherized and prepared for operation are placed close together side by side. After incising the skin of each from the level of the lower margin of the cricoid cartilage to the upper end of the sternum in the ventral mid-line, the adjacent cutaneous margins are brought together and held with clamps. The deeper tissues are separated in the mid-line down to the trachea, and the adjacent edges brought together and fastened in a manner similar to that practised upon the skin. The common carotid artery of the animal chosen for the host, on the side next to the donor, is freed for several inches. It is temporarily occluded below and permanently ligated above; then it is divided, just central to the ligature, and the end prepared for suture. The common carotid artery, on the side of the donor next to the host, which furnishes the chief blood-supply of the thyroid lobe that is engrafted, is freed for a considerable distance, and is temporarily clamped just below the origin of the thyroid branches. It is ligated below, and divided just distal to the ligature. After preparation, the end is

* Operation performed with Dr. A. H. Ryan of my staff.

sutured to the previously prepared end of the carotid artery of the host. During this period the thyroid lobe has been supplied with blood circulating backward from the distal end of the carotid artery, in virtue of the anastomotic connections of the artery, an important one being that at the base of the brain.

That the abnormal circulation of the thyroid lobe during the period of occlusion is undoubtedly adequate to sustain the vitality of the thyroid tissues cannot be questioned; for after permanent ligation of the carotid arterial trunk below the major thyroid vessel, thyroid tissue has been observed to persist in apparently normal condition.

The internal jugular vein, which should, in the case of the donnée, be chosen on the side next the donor, should be freed for some distance and temporarily occluded below and permanently ligated above. It is then divided central to the ligature, and the end prepared for anastomosis. The internal jugular vein of the donor, on the side supplying the thyroid lobe that is to be engrafted—that is, on the side next the host—is freed and temporarily occluded just below the mouth of the lowest thyroid branch. It is a fortunate circumstance if, in the case selected for operation, the inferior thyroid vein branches from the internal jugular vein. This is not always the case, for it sometimes empties into the subclavian vein. The permanent ligature is placed about the internal jugular vein some distance below the temporary occlusion, and the vessels divided just distal to the ligature. The end of the vein is then prepared for anastomosis, and is sutured to the end of the previously prepared jugular vein of the host. During this operative period venous return from the thyroid lobe is possible by means of the anastomotic connections to the veins above the upper point occluded. A ligature is passed around the common carotid artery and internal jugular vein, distal to the origins of the thyroid branches. The temporary clamps are removed from the trunks of the newly constructed vessels, and the ligature immediately tied. By this procedure the host's circulation through the thyroid lobe is established. Another ligature is now passed and tied distal to the ligature above the thyroid vessels, and the artery and vein divided between the two. The thyroid lobe is now freed from its original possessor, and is carried to the host in the situation previously prepared for its reception. The transplanted lobe is fastened in place by suitable ligatures, as described for the transplantation of the kidney. Care must of course be taken to avoid kinking or

twisting the blood-vessels. The wound is then closed in the ordinary fashion, and the dressing applied.

Attention is called, again, to the time of removal of the temporary hæmostatic clamps, for if the circulation be established through the sutured vessels very long before the artery and vein are ligated above the thyroid branches, a serious loss of blood from the host into the vessels of the donor may occur. This undesirable complication would, of course, assume serious proportions more rapidly if such premature establishment of circulation was through the artery alone; for if the vein is released at the same time, it will transmit venous blood from the donor into the vessels of the host. But whether or not the amount of venous blood transmitted from the donor to the host would equal in volume the arterial blood lost from the host into the vessels of the donor is a question. It would seem that this would vary with the relative conditions of the blood-pressure in the vessels of the two animals. But assuming that the amount of blood lost by the host was compensated for by the blood from the donor to the host, it is by no means certain that such an admixture of blood from the donor with that of the host would be desirable; for it is well known that the introduction of blood from one animal into the circulation of another is not to be regarded as a harmless proceeding. A fuller discussion of the question of blood transfusion may be found on p. 252.

Transplantation of the Parathyroid Bodies.

The parathyroids have not been transplanted with preservation of circulation through their blood-vessels excepting along with the thyroid lobe, while in transplantation of the thyroid the parathyroid tissues have always been included. According to anatomists, at least a portion of the blood-supply of the parathyroids is derived from the inferior thyroid arteries; and as these vessels are branches of the thyroid axes they are not preserved in thyroid transplantation as the operation is usually performed. But since it is claimed that the parathyroids receive blood by way of anastomotic connections with vessels of the thyroid in the vicinity of the former, and, indeed, even perhaps from the direct branches springing from the superior thyroid artery, it seems clear that in such operations a very considerable parathyroid blood-supply is preserved.

Transplantation of Ovaries.

The ovarian vessels themselves are too small for direct anastomosis, so recourse is made to the transplantation of segments or flaps (p. 77) of the parent blood-vessel—*i.e.*, the aorta and vena cava. The ovaries are separated from surrounding attachments, and a strip of tissue containing the vessels is cut out to the junction of the vessels with the aorta and vena cava. Segments of the latter are removed, and then engrafted between the ends of similar vessels previously isolated, divided, and prepared, on the host (p. 201). The ovary is placed and fixed into the situation prepared for its reception. If complete functional results are included in the object of the operation, the ovary should be placed adjacent to the ovary of the host; or the latter is previously removed, and the engrafted ovary placed in its site.

Transplantation of the Heart.

The technique of the operation is complicated by the fact that the heart normally receives a double blood-supply, the nutritional supply through the coronary arteries, which arise from the root of the aorta, and the functional supply, which reaches the right side by way of the vena cava, and the left side by way of the pulmonary veins. If it is desired to transplant the organ with maintenance of the nutritional circulation, ligate one branch of the vena cava and temporarily clamp the other near the heart, and divide them distally to the clamp and ligature. The end temporarily occluded is prepared for anastomosis. The pulmonary artery is ligated near its origin, and divided peripheral to the ligature. The pulmonary veins are ligated either singly or in mass, and divided between the ligature and lungs. The aorta is temporarily clamped near the heart, and divided peripherally to the clamp, and the end prepared for anastomosis. The organ may or may not be removed from the pericardium. It is then placed in the situation previously prepared for its reception, say in the carotid triangle. Suitable vessels in this region having been prepared, such as the central ends of the common carotid artery and external jugular vein, the end of the aorta is anastomosed to the artery and the prepared end of the superior vena cava to the external jugular vein. The clamps are then removed and the circulation through the coronary vessels established.

But a more complex method, providing both nutritional and

functional circulation, is to be preferred if the functional working of the engrafted organ is to be studied; for by the method just described the cavities of the heart are incompletely and inadequately supplied with blood, and the connection for the functional circulation, between the right and left side of the heart, is obliterated. To perform this operation the technique above described is followed, only, in addition to the vena cava and aorta, the pulmonary artery and a pulmonary vein are temporarily clamped, divided, and prepared for anastomosis, the organ removed and placed in a suitable situation in the host, which may be the anterior surface of the neck, which has been prepared for its reception. This is done by opening up the tissues down the mid-line to the trachea, freeing one common carotid artery—say the left—for a considerable space and temporarily occluding it on either side of the isolated portion, dividing between the points of occlusion, and preparing both ends of the artery for anastomosis. Also the internal jugular vein on the opposite side, or, if this be quite small, an external jugular vein, is isolated for a considerable space and temporarily occluded at either side of the isolated portion, which is then divided midway between the temporary clamps, and the ends prepared for anastomosis.

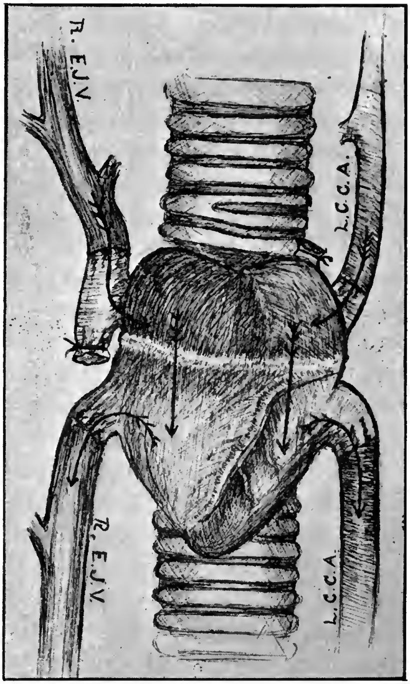


FIG. 101.—DIAGRAM OF CONNECTIONS IN ENGRAFTING HEART INTO NECK.

Arrows indicate direction of blood-currents.

The aorta is anastomosed to the central end of the common carotid artery, since it normally sustains a high blood-pressure, and since the pressure in the central end of the carotid is of comparable magnitude; also because the coronary arteries must be supplied with arterial blood under such a pressure for the adequate

nutrition of the heart. A pulmonary vein, prepared for anastomosis, is sutured to the peripheral end of the common carotid artery, thus meeting the condition of furnishing an arterial blood-supply to the left auricle and ventricle under a pressure less than that of the general arterial system. Such blood is supplied through a reversed circulation through the peripheral end of the common carotid artery by way of its free anastomotic connections, such as those situated at the base of the brain. The vena cava is anastomosed to the peripheral end of the jugular vein, thus meeting the conditions of entry of venous blood into the right auricle. The pulmonary artery is sutured to the central end of the jugular vein. The condition thus established for the pulmonary artery is abnormal in that it has an abnormally low resistance to work against. This may in part be overcome by dividing the other carotid artery or internal jugular vein, and anastomosing the pulmonary artery to the peripheral end of one of these vessels.

Transplantation of a Leg.

In carrying out this operation, the principles governing all such procedures are rigorously observed. Difficulties not present in the operations previously described are encountered, not only at the time of operation, but during the post-operative and convalescent period.

To give the various technical procedures due emphasis, and to render their purposes clearer, an account of the most prominent of the difficulties will be given before proceeding to the description of the operation itself.

In the first place, the unavoidable mutilations in such an operation are far greater and of more serious character than in the transplantations previously described. This is perhaps more clearly understood when it is remembered that even in such an operation as one involving the opening of the abdominal cavity from the apex of the sternum to the pubes, excepting for the skin, very few tissue elements are transversely divided. And such elements are chiefly of the connective-tissue variety, especially when the incision is carried through the linea alba. The magnitude of the subsequent mutilations naturally varies with the organ transplanted and with the method employed, while in the case of the limb, not only the skin and fibrous connective tissues are transversely divided, but all other tissues, such as muscle and bone, are divided. Not only is the variation one of differences in the

nature of the tissues divided, but perhaps of more serious import is the question of the relative magnitude of the mutilation. This is illustrated by actual comparisons, as in the abdominal operation described in the transplantation of a kidney, and the mutilation produced in transplanting a limb when the incision is carried through the middle third of the thigh. Of course, actual measurements vary with different animals, owing to the difference in the ratios of the measurements. In man the distances between the sternum and pubes may be 30 centimetres, and the circumference of the middle of the thigh around the skin may measure 50 centimetres. Thus the cutaneous mutilation in this instance would be much greater for the limb than for the subcutaneous tissues.

Next the muscles may be considered. In case of the abdominal operation no muscle fibres need be transversely divided. But in the case of the thigh the cross sectional area of divided muscular tissues is very great. The same is also true of bone. Also, the magnitude of lymphatic vessels and of nerves divided is much greater in the thigh operation. The bearing these factors have upon the success of the operations are in part bacteriological and pathological, owing to the much greater risk of infection in case of the thigh, due to the greater area of raw tissue surface exposed: in part surgical, from the complexity of the technique of the reunion of the parts; in part constitutional, owing to the likelihood of induction of shock due to the magnitude of the mutilation; and in part post-operative, due to the difficulty of immobilizing the part, which is especially true in the case of laboratory animals. These conditions hold when the limb is engrafted on to the stump of the thigh of another animal. And, of course, certain of them, such as great proneness to shock, would not necessarily hold to the same extent for the reasons given if the limb is transplanted into some other region, such as the neck. The operation of transplantation of the limb of one animal on to the stump of a limb of another animal will now be described.

To reduce the danger of infection of the dressings by urine, it is well to choose a female animal as host. Young adult animals, with limbs of as nearly equal dimensions as possible, in good condition and of fair size, should be selected; for such animals not only as a rule better withstand the operation, but the tissues adapt themselves to the abnormal conditions, and healing occurs more readily than in old animals. And better functional results may be expected, owing to the greater regenerative powers and

adaptability of younger tissues. Animals of fair size are selected, owing to the greater difficulty in anastomosing the blood-vessels of the limbs of small animals, the vessels being correspondingly small.

Among the chief of the considerations in deciding upon the place of operation are : Mass of tissues to be divided ; liability of interference with vascular connections in the stump, or, in the engrafted portion of the limb ; ease of applying and maintaining dressings ; and favourability of restitution of function.

It is obvious that in any given case it is impossible to optimally fulfil all of these conditions, so it is necessary to carefully consider each condition, and to weigh the seeming advantages and disadvantages in making the section at different levels in determining upon the site of operation.

Considering such an operation upon the hind-limb of a dog, we may at once decide upon either the thigh or leg. For if the section be carried through a joint, a good functional result cannot be expected ; for even though the operation be successful and the animal recover, the operated limb would be stiff at this joint. Next, comparing the leg and the thigh from the standpoint of suitability of vascular trunks for anastomoses, the thigh seems to present advantages over the leg ; for not only is it possible to select the level in the thigh which presents a single major arterial trunk, but the vessel is larger than the vessel in the leg, and it presents a longer section free of important branches. This vessel is the femoral artery, and the segment that may be freed for operation extends from the mouth of the profunda to the mouth of the anastomotica magna. If the femoral artery is occluded below the mouth of the profunda, the thigh will still receive an abundant supply of blood. And, indeed, the leg and foot may be only temporarily affected by anæmia, as there are very free anastomotic connections with the arteries of the leg. Alongside the femoral artery lies the femoral vein, and it presents an arrangement of branches similar to that of the artery. So at this level the thigh presents an arterial and venous trunk suitable for anastomosis. Nerve trunks commonly closely correspond to the major vascular trunks, and this is sufficiently true in the thigh to adequately meet the conditions of the practical requirements of the proposed operation, as the sciatic nerve represents the major pathway for nervous impulses to and from the leg and foot.

Since the lymphatic vessels are numerous, and since there are

no major trunks that can be successfully anastomosed, they are practically disregarded in so far as being a prominent consideration in the operation is concerned. The bony tissue consists of but a single stem, and there are no considerations contra-indicating operation upon it in this region.

The relatively great size of the muscular mass in this region, and the necessity of its transverse division, is perhaps the greatest objection to the selection of the thigh for operation; for not only does such procedure result in the production of a large area of raw tissue surface, but undesirable oozing of tissue juices is inevitable. But since numerous lymphatic- and blood-vessels are distributed throughout the mass, conditions are favourable to undesirable oozing of their liquid contents. Therefore, for these reasons, the conditions, after the engrafted limb is in place, are not altogether perfect for unblemished union of the two surfaces.

Furthermore, the surgical procedures necessary for the union of the parts, from the standpoint of approximating the ends of similar muscles in order to obtain most perfect functional results, and the greater danger or likelihood of infection of the wound during the operation, complicate it. And since a relatively large amount of foreign material, such as sutures, must be introduced into the wound, the operation at this level, for the reason just given, is perhaps more undesirable than in a region presenting a lesser mass of grosser structures, such as the ankle, in which region the whole groups of muscles may be handled by means of their tendons.

But since the objections do not prohibit successful operation at the level of the middle of the thigh, and since the major considerations—namely, the size and character of the vascular trunks, and the distribution of the nerve trunks—favour the operation at this point, it is rational to select it as feasible for operation. And, considering particularly the character of the vascular trunks, the exact level is fixed at about, or slightly below, the middle of the thigh.

The operation is performed by preparing two animals in the usual way as regards anæsthesia. The leg of the host and the leg of the donor on the same side are thoroughly shaved downward to below the knee. The shaving operation, as in all other operations where shaving is necessary, is carried out in a thorough manner, and the stroke of the razor is in the direction in which the hairs naturally lie. But the razor should be handled gently, so as not to remove

the cuticle itself, nor to produce abrasions of the skin, as such roughness is unnecessary for cleanliness, and abrasion of the skin is not only unnecessary mutilation, but actually introduces an additional source of danger—namely, another opening for infection is created. The unshaved portion of the leg and foot being prepared for operation are enclosed with a napkin moistened in an antiseptic solution (say 1 in 1,000 bichloride of mercury), and over this is firmly and smoothly applied a sterile roller bandage, which is laid to a point on the shaved portion of the leg some distance above the upper margin of the unshaved portion. The end of the bandage is securely fastened, so that when the protective dressing is finished, there may be no danger of it slipping or becoming disarranged during the manipulations to which it is subjected during the operation.

The animals are adjusted on the tables and covered with operating cloths, which are carefully adjusted about the top of the thigh near the upper margin of the shaved area, thus leaving the limbs to be operated upon exposed above the cloths. If possible, two operators begin at the same time, one upon the host and one upon the donor.

The operation upon the host is performed in the following manner: The limb being extended and held in position by an assistant, a longitudinal incision is made in the skin parallel to and a little to one side of the femoral vessels. The incision is made to extend above the line of the proposed section, so as to expose the vessels to within a short distance of the profunda branches, and it is carried downward to the origin of the anastomotica magna. The vessels, together with the remaining nerves and other tissues, are then separated as a strip. All branches found upon the course of the vein and artery between the profunda above and the anastomotica magna below are doubly ligated near their origins and divided between the ligatures. A temporary clamp is placed upon this strip of tissue near the profunda vessels, so as to occlude the femoral artery and vein. But the artery and vein may be separately clamped. The strip of tissue is ligated in mass just above the anastomotica magna. The vessels and accompanying tissues are then divided a little above the ligature, and the ends prepared for anastomosis. With an assistant holding the limb in position by grasping the foot and limb about the dressing, a cutaneous incision is carried completely around the thigh slightly below the level of the proposed section of bone. The muscles and other structures are similarly divided down to the bone in the same level,

and all bleeding-points are seized with forceps and ligated with fine silk. The periosteum is now divided in the same level, and carefully pushed upward for the space of $\frac{1}{2}$ to 1 centimetre, thus forming a kind of cuff. The bone is now divided transversely near the upper margin of the surface exposed by turning back the periosteal cuff and the amputated member removed. The raw tissue surface is now protected by placing two soft lint-free towels across the end of the stump in such a manner that only the end of the bone is exposed. Now using a drill having a diameter of about 2 millimetres, a transverse hole is bored through the bone at a distance of about 3 to 5 millimetres from the end. This hole may be drilled before the bone is sectioned, in which case it is well to leave the drill in place after the hole is made, in order to serve as a guide in sawing the bone. Also, if desired, another similar transverse hole at a slightly different level to the previous hole may be made in the anterio-posterior direction. The stump is now ready for the limb that is to be engrafted, which should be at this time in readiness, so that no pause in the operation will occur.

The operation on the limb of the donor is performed in the same manner as that just described for the host, with slight modifications, which are as follows: The vessels are temporarily clamped just above the anastomotica magna, ligated below the profunda branches, and divided just below the ligature. Thus, also considering the level of the division of the vessels on the host, it is plain that the surplus lengths of vascular trunks are provided both on the host and on the limb to be engrafted. This is for the purpose of allowing for retraction, which is such a constant phenomenon, especially in divided arteries, and which may result in a surprising degree of shortening. Also, it is observed that an accompanying tissue mass is preserved along with the vessels. The object of this is chiefly to provide a means of anchoring the vessels together for combination, so as to reduce the traction upon the anastomoses to a minimum.

The muscles are divided on the level of the cutaneous incision, or a little above it. Care must be taken to ligate all bleeding-points of the peripheral raw transverse surface thus exposed, as in the case of the central surface in the host. The periosteum is divided on the level a little above the line of division of the muscular tissues, and a cuff turned downward as in the case of the cuff upward on the host. Although the only connection at this time between the peripheral and central portions of the limb is the bone, considerable

bleeding may occur from the lower surface, which indicates a surprisingly free circulation through the vessels of the bone. The hole or holes corresponding accurately in direction and position to those in the end of the bone of the host are then made, considering, of course, the level at which the bone is to be divided. The bone is now divided at the level of the division of the muscles, the limb removed, and the raw surfaces protected with towels, as in the case of the stump of the host.

The operation of attaching the limb to the stump is now begun. A piece of annealed iron wire, measuring from 1 to 2 millimetres in diameter, and about 10 centimetres long, is thrust through each of the holes drilled in the ends of the bones, so that the shank of the bone occupies the middle portion of each piece of wire. The

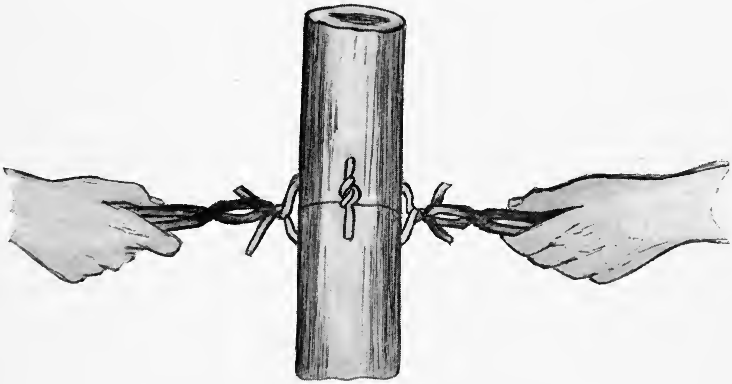


Fig. 102.—Method of Wiring Bone.

ends of the bone are then approximated, and the corresponding ends of the wire on either side of the line of the bone are symmetrically twisted together with the fingers. Using flat-nosed pliers about 6 inches in length, the wires are further twisted until all surplus is taken up and the ends of the bones firmly drawn together and fixed. Now with a pair of end-cutting pliers the twisted wires are divided away from the side of the bone, so that only about two twists remain holding the bones together—that is, the twisted ends are cut off within about 5 millimetres of the surface of the bone. Next the periosteal cuffs previously turned back on the ends of the bones are unfolded, so that they cover the line of union and come together, which restores periosteal cover for the bone. Using a medium to fine catgut suture, the tissues, which

are chiefly muscular, underlying the femoral artery and vein, are sutured together, care being taken to close all spaces so that no crevices remain. Immediately beneath the bed in which the blood-vessels will lie when sutured together, the aponeurotic surface of the muscular tissue is carefully sewn, so that it may form a smooth, continuous surface. After such a bed is formed, the blood-vessels, together with their accompanying mass of tissue, are brought into position. Any surplus length is removed, and the ends of the vessels are anastomosed in the regular manner, after which the temporary clamps are removed and the circulation restored. Immediately upon re-establishing the circulation in the peripheral portion of the limb, hæmorrhage may occur from vessels from the cut surface of the engrafted limb, and all such are immediately ligated until the wound remains dry. Beginning now at the bone, the tissues are sutured together. When the level of the sciatic nerve is reached, the ends of the nerve are sutured together by means of a single fine silk thread, which transversely penetrates the trunk near the cut ends. The remainder of the tissues are then sutured, care being taken to sew them together from the bottom of the wound outward, so that no dead space may remain. When the subcutaneous aponeurotic tissues are reached, these are carefully sewed together with a continuous suture around the entire circumference of the limb; but it is a good plan to interrupt it at several points in order to allow for swelling. The tissues that normally overlie the blood-vessels are carefully united, care being taken to see that the blood-vessels themselves are in no way compressed, and that they are not kinked or twisted. The subcutaneous tissues and skin are then smoothly sewed together around the circumference of the limb, and also where they are longitudinally parallel with the course of the blood-vessels. This finishes the operation proper.

The field of operation is now sponged off with alcohol and dusted with iodoform or boric acid, and a dressing of gauze covered by cotton, a roller bandage, and finally a plaster of Paris bandage, is applied. The cotton bandages are applied not only to the limb from below the knee to the hip, but also around the lower part of the trunk and up to the level of the diaphragm at least, so that when the plaster of Paris has set, the animal's trunk and part of the leg are securely fixed together. The operated leg is held in a semi-flexed position until the cast has set. Great care is taken in applying the bandages to avoid unequal pressure at any point;

a thick dressing of cotton is used, so that actual pressure upon a given area is not rigid, and, even though swelling occurs, pressure of the dressing will not become excessive. Also great care is taken to apply the dressing in such a way that the chance of contamination by excreta will be reduced to a minimum.

Transplantation of Arm.

This operation is performed in essentially the same manner as that described for the leg, the only variation being due to the difference in anatomical formation. The general similarity of the blood-vessels and other anatomical structures of the two regions would fix the level in the arm above the elbow, in the region between the superior profunda and the anastomotica magna arteries.

Transplantation of Pelvic Girdle.

The operation is performed by anastomosis of the abdominal aorta at a level between the inferior mesenteric artery and the iliac bifurcation and the vena cava at the same level. This operation presents the advantage of not necessitating the division of bone, and the further advantage of large vascular trunks. But against these advantages are the disadvantages of great magnitude of tissue mutilation, including much nervous tissue—that is, the sciatic plexuses—which disadvantages introduce grave possibilities of shock and infection.

The operation is performed as follows: Two young animals of equal size are selected, the one intended for the host being a female, and the donor also preferably a female. They are prepared by anæsthetizing and shaving the trunks around the entire circumference from above the level of the kidneys backwards. The roots of the tails are also shaved, as well as the legs and thighs well down to the knees. The animals are suspended upon perpendicularly placed table-tops, and fastened in position by the hind-legs. The table surface should be placed at an angle so that the body of the animal will lie upon it.

The operation on the host, the animal resting upon its abdomen, is begun by making the transverse cutaneous incision at a level just anterior to the crest of the ilium on either side. The incision in either case beginning at a point on a line drawn parallel to the vertebral column, so that it passes through the junction of the root of the tail to the trunk on either side, is carried outward to the point where the skin of the flank turns under the abdomen and comes

in contact with the surface of the table. Next, a longitudinal incision, beginning at the inner margin of the transverse incision, is carried backward to the root of the tail on either side, from which point they are connected in a circular manner around and a little outside of the outer margin of the brim of the pelvis, so that they come together at the apex of the pubic arch. Using a thin-bladed knife, the iliac bones are separated from their fibrous articulations with the sacrum, and the tissues are completely divided around the inner margin of the pelvis, leaving the pelvic organs suspended from their dorsal attachments. Corresponding to the transverse skin incision, anterior to the iliac crests, the tissues lying exterior to the longitudinal incision extending backward from this point on either side of the spinal column are transversely divided, and the deeper abdominal wall divided outward at the ends of the transverse skin incision. The animal is now turned on the board so that its abdominal surface is outward, and the transverse incision in the skin and other tissues of the abdominal wall are carried inward until they meet at the mid-line. The aorta and vena cava are now exposed and clamped just below the level of the inferior mesenteric artery, and a ligature is placed about both vessels just above the iliac bifurcation, and the vessels divided above the ligature. The exterior iliac vessels are then ligated and divided peripherally to the ligatures. By this method, owing to the free anastomotic connections between the vessels on either side of the ligatures placed just above the iliac bifurcations, a collateral circulation is provided in the peripheral trunks sufficient for the tissue demand. This is true even when the exterior iliac vessels are not ligated, so, since the latter are tied in this operation, an adequate circulation to the pelvic structures and tail of the host is assured. Next, the other tissues internal to the dorsal longitudinal incisions along either side of the sacrum are separated, and the incision continued around the margin of the pelvis; the nerves are divided. Care must, of course, be taken to avoid injury to the ureters or other pelvic structures that are to remain connected with the host. The pelvic girdle and limbs are now removed, and the host is ready for the similar tissue mass which has by this time been removed from the donor.

The operation for removing the pelvic girdle from the donor is, in its general features, identical with that of the operation on the host. But certain modifications are employed—namely, the longitudinal skin incisions are carried a little closer to the mid-line,

and follow more closely the inner margin of the pelvis, for in so doing a generous amount of this tissue may be preserved, which insures that the cutaneous surface of the host may be continuous without gaps or undue stretching after the transplantation is made. The blood-vessels are temporarily clamped near the iliac bifurcations, ligated above, and divided just distal to the ligature. Great care is exercised to avoid any injury to the peripheral portions of the vessels in removing the tissue mass from the donor.

The mass detached from the donor is now slipped into place on the host, which is lying upon its abdomen, and, by two operators, union is rapidly effected. Beginning on either side at the crests of the ilium, the fibrous tissues of the anterior and dorsal margins of the bone are stitched to the corresponding tissues along the side of the sacrum. The stitches include the aponeuroses, and are carried inward along the posterior margin of the pelvis to the mid-line of the arch, thus uniting the tissues of this region. The skin overlying the sutures thus far placed may then be rapidly sutured from the crest of the ilium on either side to the pubic arch. But since in all transplantations the question of period of anæmia is a most important consideration, owing to its direct bearing on the question of survival of the engrafted tissues, and also since the circulation must be restored before coagulation of the blood in the vessels of the tissue mass occurs, it is better to suture only such tissues as are necessary to fix the mass in place and such tissues as must be sutured in order to make a bed for the blood-vessels before suturing the vessels themselves and re-establishing the circulation. The animal is turned upon its dorsal surface, and the blood-vessels anastomosed and the new circulation established. The ventral margins of the tissues divided along the lateral margins of the sacrum are sutured together. All divided peritoneal margins are smoothly united with fine sutures. Beginning at the outer terminations, the transverse incisions of the muscular wall of the abdomen are sutured, the sutures being tied together in the mid-line. The corresponding subcutaneous tissues may then be sutured, and the transverse abdominal skin wound closed. If the dorsal cutaneous incisions have not been repaired, the animal is turned upon its ventral surface and the work performed. This finishes the operation. A dressing such as described for the thigh is then applied to encase the trunk and legs.

Transplantation of the Posterior Trunk, together with its Contents and Appendages.

A large animal is selected for host, and a small closely related one for the donor. A bitch and a pup would meet the conditions. The host is prepared by exposing one carotid artery and jugular vein by a median incision, and dividing them and preparing the central ends for anastomosis. The mass for engrafting is removed by another operator at the same time. This is done by opening the thorax from above downward to the level of the anterior margin of the diaphragm, which is the level of the proposed cross-section, and freely exposing the viscera contained in the cavity. The œsophagus is doubly ligated near the diaphragm and divided between the ligatures. The branches given off from the descending aorta and vena cava near the diaphragm are ligated. The aorta and vena cava are temporarily clamped near the diaphragm, and ligated some distance above. They are then transversely divided below the ligature and the peripheral ends prepared for anastomosis. The branches between the level of section and the temporary clamps are then divided distal to the ligatures. The trunk of the animal is then divided at the level of the upper margin of the diaphragm. The ends of all large vessels appearing in the peripheral surface of the cross-section are ligated. The ligated end of the divided œsophagus on the anterior surface of the diaphragm is further prepared by turning the walls inward and securing with a fine suture, so that only the tissue of the outer surface of the wall are exposed. The tissue mass is then placed in position on the neck of the host. The spinal column may be firmly sutured to the manubrium of the sternum, and the dorsal muscles are sutured to the tissues of the host just anterior to the manubrium. The aorta is sutured to the carotid artery and the vena cava to the jugular vein. If the internal jugular vein is small, the external may be used. The median muscular incision in the host is sutured from above downward, but the suture is discontinued and tied before the sutured vessels are encroached upon. The upper margin of the thoracic wall is now firmly sutured around its entire circumference to the muscular tissues of the host's neck. The edge of the skin of the engrafted mass is then sutured to the edge of the skin of the host around the entire circumference of the engrafted mass and of the wound of the host. This completes the operation.

Transplantation of the Neck and Head, together with their Appendages.

As in the preceding case, a larger animal is selected for host than for donor, in order to minimize the strain on the circulatory mechanism of the host. The operation may be performed by removing the head from the donor, and immediately engrafting it upon the host. But owing to the great susceptibility of the brain to anæmia, and to its relatively low power of recovery, unless the operator is sufficiently skilful to enable him to re-establish the circulation well within half an hour, the operation should be performed without complete interruption of the circulation. The animals being prepared, are placed close beside each other, so that the manubrii of the sterni are in the same transverse level. The anterior surface of the neck of each is laid open in the mid-line by a longitudinal incision from near the cricoid cartilages to the manubrium of the sternum. At first only the skin is incised, and the edges along the adjacent margins of the wounds are sewed together. The deeper tissues are then separated in the mid-line down to the trachea. Segments of the common carotid arteries on the adjacent sides of the two animals are isolated and prepared for anastomosis. The artery of the host is ligated above and the central end prepared, and that of the donor is ligated below and the peripheral end prepared. The adjacent external jugular veins of the two animals are similarly prepared, and the corresponding vessels of the two sutured together.

The internal jugular veins and the vertebral arteries of the donor are next doubly ligated and divided between the ligatures. Then the as yet unoperated common carotid artery and external jugular vein are similarly treated. The muscles and other structures are now transversely divided down to the spinal column. The circulation through the anastomosed vessels from the host are now released, but if prior to this time alarming symptoms from deficient cerebral circulation appear, the new circulation from the host should immediately be established. The spinal column, together with the cord, are now divided, which is readily accomplished with a small thin-bladed knife. In fact, the cutting part of the complete head amputation is performed with this knife. Hæmorrhage from the surface of the engrafted head is carefully controlled, after which the mass is attached to the host by suturing the end of the vertebral column to the manubrium of the sternum, and the

cut ends of the muscles of the neck to the anterior surface of the muscles of the neck of the host. The longitudinal incisions in the anterior mid-line of each are closed down to the margin of the transverse surface of the neck of the mass being engrafted, including the skin. The cutaneous margins of the mass and of the host are then evenly sutured together, which ends the operation. The dressing, which is laid over the wound, is well padded with cotton, and the whole encircled with roller bandages, which encircle both necks up to the cranii. Over this is placed a tailed bandage extending back on the thorax of the host, and the ends are tied along the dorsal mid-line of the host (see p. 250).

Parabiosis, or the Engrafting of Two Animals Together.

There are several ways by which this operation can be performed, but the method described is perhaps the best.

Two animals of equal size are prepared for operation, and placed closely side to side in the same transverse level. The adjacent sides having been shaved and prepared, a longitudinal cutaneous incision is made in the adjacent sides of the necks, and the dorsal margins stitched together. The adjacent carotid arteries are exposed by separating the muscles, and segments of each are isolated. The central end of one and the peripheral end of the other are prepared and anastomosed together. The corresponding internal or external veins are similarly prepared and connected, and the crossed circulation established, the character of the blood to one animal being arterial, and to the other venous.

The opposed muscular margins are then sutured together around the margins of the wounds, and also the remaining unsutured cutaneous margins. For the better fixing of the animals together the neck incisions may be prolonged backward along the sides and the resulting cutaneous margins on each animal sutured to the corresponding ones of the other animal; or such incisions may be made in the skin of the sides independently of the neck incisions.

The dressing is covered with an extensive plaster bandage, or with a strong cloth, tailed bandage, so that the necks and trunks of the two animals are firmly bound together.

Results of Replantation of the Thigh.

The operation was performed on about an 8-kilogramme white dog, under ether. Circular incision of the skin was made immediately below the knee and the internal saphenous vein ligated. A

second incision, perpendicular and continuous to the first one, was made along the femoral vessels as far as the upper part of Scarpa's triangle. The skin about the circular incision was dissected and retracted upward as far as the lower part of the thigh. The edges of the skin on either side of the longitudinal incision were dissected for about $\frac{1}{2}$ inch, the femoral aponeurosis exposed and opened, and the femoral vessels and nerve dissected and severed at the middle portion of the thigh. Section of the sartorius and femoral quadriceps was made about 3 centimetres above the knee. Also section of the sciatic nerve and of the biceps, semitendinosus, internus rectus, adductor longus, and semimembranosus muscles, was performed at different levels. Afterward the femur was cut at the union of its lower and middle thirds. The limb was then removed and enveloped with sterilized moist compresses.

After a few minutes the amputated portion of the limb was placed on the operating table close to the remaining stump of the thigh.

The continuity of the artery and vein was immediately reestablished by end-to-end suture. The two ends of the bone were closely approximated and sutured together with silver wire.

The temporary hæmostatic clamps were then removed and the circulation immediately restored through the peripheral parts of the artery and veins. Absolutely no blood escaped from the vessels at the lines of anastomoses. The pulsations of the popliteal artery immediately became normal, and the femoral vein filled with circulating venous-hued blood. The peripheral end of the cut muscles began to bleed slowly.

The cut ends of the sciatic nerve were then sutured together with silk, and the muscles, aponeurosis, and skin with catgut. The line of cutaneous sutures was covered by a dressing of gauze and collodion. Afterward the lower portion of the abdomen, hip, thigh, and leg were enveloped with cotton and a large plaster of Paris bandage.

Before putting on the dressing the state of the circulation in the limb was examined. The pulsations of the popliteal and posterior tibial arteries were as strong as the pulsations of the same arteries in the other limb. In hue, the replanted foot was a little redder, and the temperature to the touch a little higher than was the temperature of the other foot and leg. The vaso-dilation was similar to that observed following the use of an Esmarch bandage.

About eight hours after the operation the animal was in good condition. The replanted foot was much warmer than the normal one, and a little general swelling of the foot had occurred.

Twenty-four hours after the operation the animal was in good condition, but the replaced foot was very much warmer than the other foot. The swelling was considerable. There was no compression of the leg by the plaster of Paris bandage, therefore the swelling was thought to be due to the section of the vasomotor nerves. During the afternoon the foot became a little cooler, but the swelling larger.

Thirty-three hours after the operation the foot was found to be almost cold. The veins were greatly distended. A small incision was made between the toes ; dark blood, and afterward red blood, escaped through the incision. The hæmorrhage was then controlled and the wound dressed.

It was thought that a progressive obliteration of the venous anastomosis was taking place, owing probably to some lack of asepsis during the operation.

Fifty hours after the operation the foot was cold and the swelling very large. No hæmorrhage occurred through a small incision in the skin. As it was considered that the development of gangrene was unavoidable, the dog was killed with chloroform.

A post-mortem examination was immediately performed, the results of which follows :

After the removal of the plaster of Paris bandage and the cotton, the gauze and collodion dressings over the lines of the cutaneous incisions were examined. The dressing of the longitudinal incision was good, but the dressing of the circular incision was strongly contracted, causing a ring of constriction around the leg, below which the skin was of a violet hue. The foot and leg were cold and markedly œdematous, while the knee, the popliteal region, and the thigh, were warm and not œdematous. No abdominal redness or swelling of the thigh could be detected.

The thigh and the leg were dissected, the sutures uniting the femoral aponeurosis cut, and the vessels examined. There was no stenosis of the artery or vein. The vessels were then opened by longitudinal incisions. The anastomoses were perfect, no clot being present, and the endothelium continuous and apparently normal.

The sutures of the muscles were cut and the ends separated. The examination revealed a satisfactory state of the union between them.

There were no dead spaces between the tissues, excepting a small one near the bone. The hue of the peripheral end of the muscles was darker than that of the central end. The connective tissue of the thigh and of the popliteal region seemed normal, while in the leg and foot below the ring of constriction it was markedly infiltrated and œdematous. The veins of the foot and leg were extremely dilated and filled with coagulated blood. The circular constriction produced by the gauze collodion dressing had stopped the venous circulation, as it sometimes happens in human surgery when a dressing is too tightly applied—*e.g.*, in the dressing of fractures. At first there may be a feeble circulation through the constricted veins, but this soon stops and the limb becomes swollen. Shortly after the arterial circulation also stops and gangrene develops.

Summarized, this experiment shows that the circulation may be easily and entirely re-established through a replanted thigh. The pulsations of the femoral, popliteal and posterior tibial arteries were as strong as the pulsations of the corresponding arteries of the other side. The arterial circulation seemingly was normal.

The capillary circulation was exaggerated, the temperature of the limb being higher and its hue redder, owing, doubtless, to the fact that the vasomotor nerves were cut.

The venous circulation was observed to be good immediately after the operation; but the post-mortem examination demonstrated that between the point of compression by the circular dressing and the anastomoses of the vessels there was neither infiltration nor œdema of the connective tissue. The hue of the muscles peripheral to the line of amputation, however, was darker than the hue of the muscles central to the line. This difference was probably due to venous congestion.

The greatest departure from normal observed in the character of the circulation of the replanted limb was dilation of the smaller vessels. It is improbable that this vaso-dilation of itself would have produced serious swelling of the limb. Doubtless the replanted limb increased in size owing to the vaso-dilation, and this would have, of course, increased the tightness of the bandage. Examination of a transplanted kidney and of a replanted thyroid gland showed both to be enlarged in size, owing probably to the increase in the circulation.*

* The above experiment is quoted from a paper by Carrel and the writer in the *American Journal of the Medical Sciences*, February, 1906.

A similar experiment, extending over a longer post-operative period, gave the following results :

The animal employed was a small white bitch. Through a longitudinal incision the vessels of the thigh were exposed and cut above the point of Scarpa's triangle. The skin was circularly severed and the thigh completely amputated above the junction of its lower and middle third. After a few minutes the limb was replanted. The ends of the bone, the muscles, the vessels, and the sciatic nerve, were united. The circulation was re-established after having been interrupted for one and a quarter hours. The pulsations of the popliteal and saphenous arteries were normal. The venous-hued blood circulated very actively through the femoral and saphenous veins. Arterial-hued blood flowed from the small arteries of the peripheral part of the limb. The skin was sutured and a plaster dressing applied to the limb and trunk.

After the operation the general and local conditions of the animal remained very satisfactory. It drank and ate normally and walked on its three sound limbs. The skin of the replanted foot remained normal, but its hue was redder and its temperature higher than that of the normal foot. The anterior part of the foot soon became moderately swollen.

Seven days after the operation the dressing was partially removed. The limb presented neither œdema nor trophic troubles. The œdema of the anterior part of the foot was doubtless due to pressure by the lower edge of the bandage, as the swelling completely disappeared within a few hours after correcting the fault of the dressing. The skin was normal and the wound was uniting, *per primam intentionem*, without evidence of inflammation. The temperature of the skin was higher below than above the line of suturing.

Eight days after the operation the foot appeared normal in size, all œdema having disappeared.

On the tenth day, during the afternoon, the temperature of the replanted foot became lower—*i.e.*, similar to that of the normal foot. The dressing was then removed. It was found that, owing to a slipping of the plaster bandage, some urine had got into the cotton dressing and caused infection of the upper part of the longitudinal incision. A small subcutaneous abscess had developed along the vessels. The general conditions of the animal were excellent, and the nutrition of the limb satisfactory. As the arterial pulsations were much weakened, and as it was considered important to accurately determine the cause of this change, the

animal was etherized and the vessels examined through cutaneous incisions, after which it was killed.

This dissection *in vivo* under ether gave the following results : The point of the vascular anastomosis was surrounded by the small subcutaneous abscess. The venous anastomosis was good. The arterial anastomosis was partially occluded by a small clot. All the other portions of the vessels appeared perfectly normal. The circulation through the limb was yet satisfactory, as the obliteration of the anastomosis was not complete. The union of the skin, the muscles, and the sciatic nerve, was normal. The process of the consolida-

FIG. 103.—REUNION OF SKIN OF AUTO-ENGRAFTED LEG AND STUMP AFTER ELEVEN DAYS (DOG).

tion of the bone was beginning. It is possible, but not certain, that, if the animal had been allowed to live, the arterial stenosis would have gradually increased, and that in the end the circulation would have been interrupted. Then no doubt gangrene of the limb would have occurred, which result would have been due primarily to the secondary infection.

Therefore, the circulation of a replanted limb, re-established an hour and a quarter after interruption, by end-to-end anastomosis of the femoral artery and vein, was adequate, as judged by the metabolism of the limb.

No trophic trouble occurred during ten days.

Healing of the severed tissues appeared to be as rapid and complete, as after an ordinary surgical wound.*

Result of Transplantation of the Fore-Leg.

May 14, 1908.—Large brown male spaniel. The right fore-leg was removed at the shoulder and replaced by a leg from another animal. The operation was completed at 5.45 p.m. The animal came out from the ether with only a slight amount of nausea. The pulse in the transplanted leg was good and the foot was warm. Soon learned to care for the foot. Seemed to be in no pain. Had several naps, between which it would move about, drink water, etc.

May 15, 1908.—Foot gradually becoming swollen ; pulse good and foot warm. Opened dressing at 1 p.m. ; wound looks good ; cut two or three stitches ; dressed with boric acid.

May 16, 1908.—Size and condition of foot about the same. Ate, and urinated freely. Changed dressing about five o'clock.

May 17, 1908.—Dog in fine condition ; apparently no change ; foot warm ; in no pain.

May 18, 1908.—Condition about the same as before ; wound in good shape ; serous fluid pressed from inner part of wound ; cleaned wound with hydrogen peroxide, and dressed with boric acid. Leg pink and warmer than unoperated leg. Dog ate well and urinated freely.

May 19, 1908.—Dog in fine condition. Dressing moist ; removed dressing. Entire leg and shoulder is somewhat larger. Sponged with bichloride of mercury solution and dressed with iodoform.

Later, owing to suppuration, the dog was chloroformed, but the records have been misplaced.

Results of Transplantation of Kidneys.

Only transplantation of renal tissue with anastomosis of blood-vessels will be considered, since a very important function of the kidney is well known to be the separation from the blood and of excretion of waste products, retention of which is rapidly detrimental or fatal to the animal. Obviously, then, to approach anywhere near to the normal conditions of such an organ it is necessary

* The above experiment is quoted from a paper by Carrel and the writer in *Science*, N.S., vol. xxiii., No. 584, pp. 393-394, March 9, 1906.

to provide a functional as well as a nutrient blood-supply, and to provide a channel for the escape of the excretions to the outside of the body; otherwise a functional test of the operation is impossible. Also, this is necessary not only for anatomical reasons (connections of tubules, etc.), but an animal cannot long survive mere excision of renal tissue in excess of three-fourths of the total amount; for, in spite of a polyuria, a fatal derangement of metabolism is said to follow. That the protein metabolism is particularly affected is indicated by the rapid wasting of the muscular tissues and large amounts of urea excreted.*

This upsetting of the metabolism has been attributed by Bradford to lack of internal renal secretion. It would seem from this standpoint that the internal secretion of less than one-half of one kidney is insufficient to maintain life. It is necessary, therefore, to engraft one-half or more of a kidney, fulfilling at the same time the requirements as to a functional circulation and to an excretory channel. A mass of tissue of this size could not possibly survive without attention to the blood-vessels, at least in any but very small animals, even if there were no other valid reason against employment of the simple method. Since it is well known that one kidney is adequate for maintaining life, and since the entire kidney is easiest to handle, such operations should be performed with the entire organ, or both.

Floresco seems to have been the first to publish a feasible method of transplanting the entire kidney with anastomosis of the blood-vessels and report successful results. He used dogs.

The kidneys transplanted by Floresco were not, so far as I am aware, successfully put to the functional test—*i.e.*, not all of the original kidney tissue was removed, and therefore his results are not conclusive.

Floresco first tried to engraft a kidney into the inguinal region, using the femoral artery and vein for anastomosis with the renal artery and vein. Such kidneys, he said, retained vitality for a day, at which time necrosis set in, which lasted from forty-eight to ninety-five hours longer. The failure of the operation was attributed principally to the unfavourable site. Next he engrafted the kidney into the cervical region, using the carotid artery and jugular vein for anastomosis with the renal vessels. In such experiments secretion of urine was observed for a week. Owing to infection and necrosis of the ureter the observations were discontinued

* *Cf.* Stowart, "Manual of Physiology," 1910, 569.

on the tenth day. The unsatisfactory result was attributed to the abnormal location of the kidney.

He next engrafted into the abdominal region. The operation was performed by removing the kidney from one dog, the host, and replacing it with the kidney from another dog by anastomosing the renal artery and veins. The ureter was made to open on the skin. Necrosis occurred in from twenty-four to seventy-two hours.

He then considered the influences of length of operation, and concluded that an hour was too long a time. Also, he compared various methods of treatment during the operation. He tried displacing blood from the kidney with 0·75 to 1·0 per cent. salt solution, and with Locke's solution. He concluded that the use of liquids to remove the blood, the liquids being of a character designed to preserve the vitality of the tissues, did not render the operation permanently successful. He considered that the necrosis observed in kidneys transplanted without perfusion was due to the intravascular coagulation. But when coagulation was prevented by perfusion with a non-coagulable liquid, the results were not much different (*cf.* p. 236).

He then tried rendering the blood incoagulable by peptone and leech extract injections. Again, he was unsuccessful in obtaining permanent results. But in the experiment in which peptone was injected, and the ureter anastomosed to the ureter, and the normal kidney removed, the animal was alive and in good condition after eight days. His longest result is shown in the following protocol:

Experiment III.—Ureter anastomosed to another ureter. Two dogs are anæsthetized with ether. The kidney of one is removed by the dorsal lumbar way; it is small. The renal vessels are dissected for a considerable distance. Urine flows through the ureter in large quantities.

The kidney of the second dog is raised up and dissected. (The urine of the dog had been analyzed before the operation.) The end of the renal artery of the first kidney is very near to the bifurcation. By means of forceps one spreads the end of the artery. Anastomosis of the vessels is made very rapidly and very easily. (The operation lasted half an hour.) On removing the forceps, the arterial flow is re-established by the superior branch of the bifurcation, which is very near the level of the anastomosis. The anastomosed vein does not present any oozing of blood. The ureter, by the orifice whence one sees the flow of urine, is anastomosed to the peripheral end of the second ureter.

In addition to what was done in the preceding experiment, the nerve of the first kidney was anastomosed to the central end of the nerve of the second kidney.

The wound washed with sterile water was closed by a three-plane suture.

Second Day.—Animal drinks water. . . . No increase in temperature.

Third Day.—The animal in good condition ; eats meat. . . . No fever. The urine is a little hard to collect ; it does not differ from that before the operation.

Fourth Day.—Animal, which is well supported, drinks milk ravenously. The dog is gay.

Fifth Day.—The wound presents only two points of suture not healed. Animal eats meat ; runs in yard.

Tenth Day.—Dog in good condition ; eats meat ; thirsty ; no fever. Wound not healed on ventral side for distance of 1 centimetre.

Fifteenth Day.—Animal is well (cured) ; eats well ; urine clear. Comes when called, and allows petting.

Sixteenth Day.—Dog again anæsthetized ; opened old wound for a short distance. Through the opening one observes the transplanted kidney. No portion is flabby, and after a short observation of the kidney the wound is washed and carefully closed.

Second Day (seventeen days after the first operation).—The animal drinks and eats well ; the wound does not present suppuration ; the dog is running in the yard.

Sixth Day (twenty-one days after the first operation).—Almost healed.

Tenth Day.—Same condition.

In this dog the right kidney was later removed.

Floresco concluded that—

1. Transplantation of kidney is very difficult, but possible.

2. Failure of the transplantation of kidney due to site and stasis of blood-vessels.

The abdominal region is the only place favourable for survival of the kidney. The depth of the organ, situation, protection by muscles, and surrounding organs and renal pressure, important factors. Such conditions found constant only here. Not present in cervical region nor inguinal region. Failure, perhaps, also due to stasis of blood, which determines necrosis of the kidney.

3. Blood stasis cannot be dispelled by the liquids which provide a

prolonged vitality of the kidney and which prevent coagulation, or are able to destroy stasis of blood. Vaseline alone, which forms a fatty coat, prevents stasis, which is the true cause which determines renal necrosis and unsuccessful transplantation of the kidney.

4. The proceedings of anastomosis termino-terminal or by imbrication are the only two good methods. (He prefers the former, which is very simple and rapid, but uses four threads, which prevents constriction of the vessel.)

A kidney which presents a bifurcated renal artery ought to be abandoned (ordinarily, of ten kidneys, there is one that presents bifurcation near the hilum). . . .

5. The nerve of the transplanted kidney is anastomosed to the end of the renal nerve of the dog upon which the transplantation is made.

6. Action of liquids, which prevent the coagulation of blood and increases the resistance of the kidney, may have a favourable influence on the transplantation of the kidney.

7. The ureter must not be fastened to the skin, as this is always a cause of infection, which determines sooner or later the death of the animal. The ureter ought to be anastomosed to the peripheral end of the ureter of the dog. The anastomosis of two ends of the ureter may start necrosis of the ureter, which may extend up to the kidney and produce death. Anastomosis of two ureteral ends ought to be made by two planes : interior and exterior.

8. The survival of a dog with a transplanted kidney has been in one case of twelve days; in another case, where on one side is a transplanted kidney, and on the other a normal kidney, the dog is well even after a month.

Later, in 1905, Carrel and I engrafted a kidney into the cervical region in a manner similar to that practised by Ullmann (p. 13), with excellent temporary results as regards the circulation and preservation of excretory function.

The kidney of a small dog was extirpated and transplanted into the neck. The renal artery was united to the carotid artery, the renal vein to the external jugular vein, and the ureter to the œsophagus. Three days after the operation the neck and the abdomen were opened in order to study the functions of the transplanted kidney, and to compare them with the functions of the normal kidney. The transplanted kidney was found adherent to the muscles, and dissection was necessary to free it. In size it was

larger than the normal kidney. Its hue was darker. To the touch the consistency of its tissue was normal, and the pulsations of its tissue were normal, and the pulsations of its artery were as strong as the pulsations of the artery of the normal kidney.

The circulation of the transplanted kidney was slightly greater than in the normal kidney, as detected by the touch, copiousness of hæmorrhage from incision in cortex, and pulse tracings.

The secretion of urine by the transplanted kidney was about five times more rapid than by the normal one. The intravenous injection of sodium chloride solution caused no change in the rate of the secretion in the normal, but markedly increased the rate of the secretion in the transplanted organ.

The composition of urine secreted by the transplanted kidney differed somewhat from that secreted by the normal one. The constituents were similar, but the chlorides appeared to be more abundant in the urine from the transplanted kidney, while the organic sulphates, pigments, and urea were more abundant in the urine from the normal organ.*

After having devised a method of transplanting tissues in mass —*i.e.*, with their surrounding structures—obtaining an adequate blood-supply by using the parent blood-vessels—*e.g.*, in the case of the kidneys—interposing segments of the aorta bearing the renal vessels between the cut ends of the corresponding vessels of the host, we practised renal iso-transplantation on dogs and cats with excellent temporary results.

Result of Transplantation of Both Kidneys from a Dog into a Bitch, with Removal of Both Normal Kidneys from the Latter.

A large-sized terrier was anæsthetized, and both kidneys and the upper part of the ureters were removed, together with their vessels, nerves, nervous ganglia, the surrounding connective tissue, the suprarenal glands, the peritoneum, and the corresponding segments of the aorta and vena cava. The mass was then placed in a vessel of isotonic sodium chloride solution, and the dog killed.

A small young bitch was then anæsthetized, and the abdomen opened through a half-circular transverse laparotomy. The aorta and vena cava were cut a little above the mouth of the ovarian vessels. The kidneys of the dog were then removed from the salt solution, and put into the abdominal cavity of the bitch, and the

* The above experiment is quoted from a paper by Carrel and the writer in *Science*, N.S., vol. xxii., No. 563, p. 473, October 13, 1905.

segments of the aorta and vena cava were interposed by biterminal anastomosis between the cut ends of the aorta and vena cava of the bitch. The circulation was re-established, after having been interrupted for one hour and a half. The kidneys immediately became red and turgid, as after a simple transplantation ; but about half an hour later the state of the circulation became normal, so that no difference could be detected between the transplanted and the normal kidneys. Clear urine flowed abundantly from the transplanted ureters, which were united to the normal ones.

Both normal kidneys were dissected and extirpated. The appearance of the transplanted and normal organs was so similar that in extirpating the latter it was necessary to examine the pedicle in order to be certain of their identity. The operation was completed by suturing the abdominal wall and applying the dressing. Two hours after the operation the animal walked about her cage. In the afternoon she drank and urinated copiously. The following day and subsequently her diet largely consisted of meat. She drank, ate, walked, and, when permitted, mingled with other dogs ; but in the latter case she was carefully watched, as she showed a strong disposition to fight. As far as could be detected, her condition was normal. The urine was clear and showed no evidence of containing blood. The total amount appeared to be somewhat increased. On the seventh and eighth days several samples were collected and analyzed, the results of which showed a slight variation in composition, but probably within normal limits. The only abnormal constituent detected was coagulable proteid, the largest amount present in any of the samples being less than 0·25 per cent. A brief result of the analysis is given below :

Urine collected on the eighth day after the operation : Colour, pale yellow ; odour, normal ; reaction, slightly alkaline ; urea, 1·95 per cent. ; uric acid, trace ; chlorides, sulphates, and earthy and alkaline phosphates, normal ; kreatinin, doubtful ; indoxyl, none ; coagulable proteid, less than 0·25 per cent. ; sugar and peptone, none (*cf.* p. 242).

It was inconvenient to collect the total urine for twenty-four hours, as it was deemed advisable to allow the animal to move about freely.*

Some of our animals lived for weeks after such operations, but all ultimately died, with well-marked uræmic symptoms. And no

* The above experiment is quoted from a paper by Carrel and the writer in *Science*, N.S., vol. xxiii., No. 584, p. 394, March 9, 1906.

one, though many experiments have been reported, has yet succeeded in keeping an animal alive for any great length of time which carried the kidney or kidneys of another animal after its own kidneys were removed.

Gross histological examination of kidneys transplanted by the writer showed a congestive, hæmorrhagic, and progressive degenerative process. In the beginning the circulatory change is greatest in the boundary zone, but later the cortex of the kidney presents extensive hæmorrhages and degeneration and disappearance of the renal cells.

There seems to be some variation in the results—*e.g.*, rate and magnitude of the pathological process. But the degenerative pro-

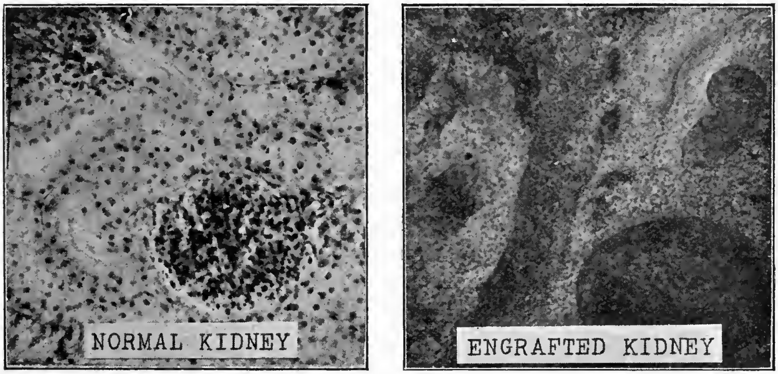


Fig. 104.—Comparison of Microscopical Appearance of the Cortex of the Cat's Normal Kidney, with an Engrafted Kidney Seventeen Days after the Operation.

cesses are progressive, a seventeen-day specimen showing much more marked degenerative changes than specimens taken after shorter intervals. In all these experiments the kidneys were subjected to complete anæmia and perfusion with saline solution, and these factors have to be taken seriously into account. In a case in which only one kidney was removed from a cat, one kidney from another cat was introduced, and appropriate vascular and ureteral connections made. This animal did well, as shown by a photograph taken about a year later. Her remaining kidney was then removed, and she died in a few days with the usual symptoms of renal insufficiency. Histologically, only traces of normal structure remain, a few glomeruli and tubules having preserved sufficient of their structure for identification. This, so far

as I am aware, is the longest observation which has been recorded on an iso-engrafted kidney, and therefore the longest instance of survival of such engrafted renal tissue.

In addition to the period of complete anæmia with perfusion to which the kidney was subjected at the time of operation, other factors probably contributed to the disappearance of renal tissue. There was more or less ureteral stenosis, but whether this was due to a lack of activity on the part of the kidney or to operative fault is, of course, unknown. The same was true of the renal blood-vessels, and, as in the case of the ureter, the primary factor in producing the condition is unknown. That the kidney still received

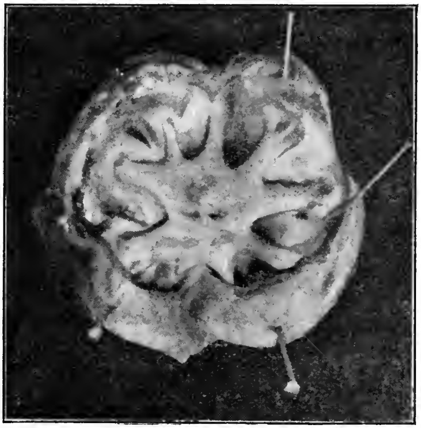


Fig. 105.—Engrafted Kidney at Post-Mortem Examination of Cat.

(*Journal of the American Medical Association*, 1908, li. 1658.)

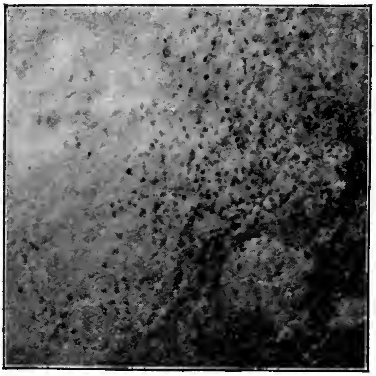


Fig. 106.—Microscopic Appearance of Kidney shown in opposite Figure.

blood is evidenced, not only by the examination at the time of the last operation, but by the presence of a relatively large mass of tissue; for when the circulation to a kidney is completely shut off, absorption soon occurs.*

Villard and Tavernier have recently reported results of transplanting kidneys without perfusion of their blood-vessels. A kidney was removed from a dog, and the end of the renal artery connected with the carotid artery and the renal vein with the external jugular vein, and the ureter was made to open upon the

* The above experiment is quoted from a paper by the writer in the *Journal of the American Medical Association*, March 12, 1910, liv. 831-834.

surface of the skin. The circulation was interrupted for one and a half hours. The urine secreted by this kidney for a time contained albumin. At the end of fifty-six days there was an abundance of albumin-free urine, and it contained 2·8 per cent. urea.

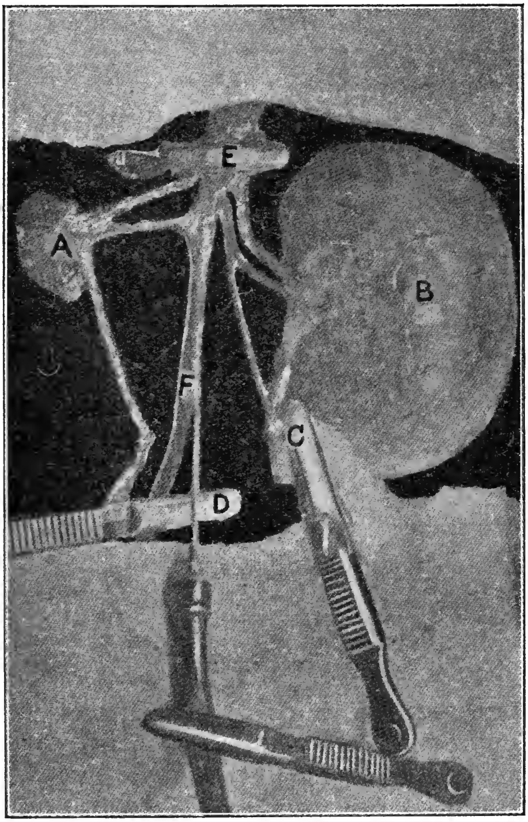


FIG. 107.—KIDNEYS AND AORTA OF CAT 22, OPERATED ON MAY 23; PHOTOGRAPHED MAY 22, ONE YEAR LATER.

A, Right kidney, rendered anæmic and perfused; B, left kidney, anæmic only; E and D, temporary clamps on aorta; C, showing method of clamping ureteral vessels; F, perfusion needle, thrust into aorta and connected by tube with reservoir holding solution (see pp. 240 and 242).

(*Archives of Internal Medicine*, 1910, v. 232.)

Another operation was performed, and the animal died sixty-eight days after the kidney was first transplanted. At the autopsy the kidney macroscopically was normal, save for a slight nephrosis and thickening of the capsule.

These investigators question the use of salt solution for perfusing kidneys for transplantation—indeed, they systematically abstain in all cases from perfusing. In substantiation of this position, which had previously been pointed out and the reasons in its support advanced by the writer, they cite the paper,* which I am permitted to quote through the kindness of the Editor.

Investigations in this direction were suggested by the character of the results following transplantation of kidneys.

The method consisted in temporarily shutting off the circulation in a segment of the aorta, including the origin of the renal arteries, and then perfusing the kidneys by injecting the solution to be tested into this segment by means of a small trocar (or needle) thrust through the wall of the aorta, the instrument being connected by means of a rubber tube with a reservoir containing the solution (see p. 23).

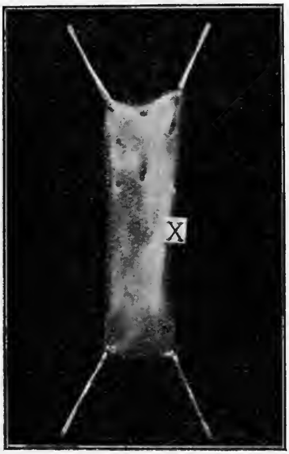


Fig. 108.—Segment of the Aorta of a Cat whose Kidneys had been perfused by thrusting a Trocar into the Aorta.

The puncture, which was made near X, is well healed.

On withdrawing the needle the puncture in the wall of the aorta was closed by several simple stitches which penetrated the coats of the vessel. The clamps (serrefines) were then removed from the aorta, and the abdominal wound closed. The animal was then bandaged and placed in the hospital.

It should be remarked that, in addition to the aorta, all arteries other than the renal arising from the segment were clamped, as well as all other vessels that might give a collateral circulation—*e.g.*, the ureters, with their surrounding tissues were compressed in mass by means of encircling coarse ligatures. (Narrow strips of cloth, temporarily fastened by means of ordinary hæmostatic forceps or serrefines, are very good for this purpose.) Even with such precautions, more or less patent connections were maintained, as shown by the fact that on withdrawing the perfusion needle, as a rule, arterial-hued blood soon began to escape from the opening.

In some of the experiments the adrenals were shut off by the anterior serrefines, and sometimes they were not, so that data

* *Archives of Internal Medicine*, 1910, v. 232.

on the results of perfusing them was also obtained. In some cases the renal artery (or arteries) to one kidney was clamped during the perfusion, so that it was possible to compare on one animal the result of anæmia alone with anæmia accompanied by perfusion. The temperature of the perfusion liquid varied in different cases, as noted in the table (p. 244). The pressure employed was, for the

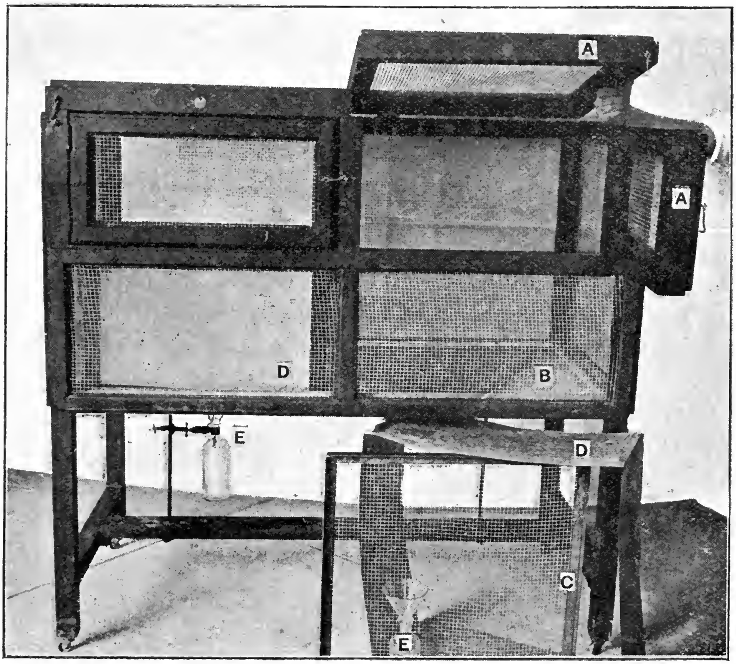


FIG. 109.—PRACTICAL FORM OF METABOLISM CAGE, CONTAINING TWO COMPARTMENTS; ONE COMPARTMENT IS ASSEMBLED; THE OTHER IS OPEN AND DISMOUNTED, TO SHOW INSIDE FEATURES.

A, Hinged door; B, funnel-shaped metal bottom; C, removable metal screen bottom, on which the animal rests; D, metal guard, which fits inside upturned flange on B; E, funnel and bottle for receiving urine. Frame finished with waterproof paint. All metal parts galvanized or tinned.

(*Cf. Archives of Internal Medicine*, 1910, v. 234.)

most part, practically constant for the non-colloidal solutions (plain sodium chloride, Ringer's and Locke's solutions); but with colloidal solutions—*e.g.*, starch—more pressure was required to force the liquid into the capillaries. In those cases in which the urine was collected the animals were kept in metabolism cages along with control cats. The diet, etc., was the same in all cases.

On beginning the perfusion, the kidneys could be observed through their capsules to become paler, the degree of paleness being taken as an index of the degree of perfusion. In addition, puncture of the kidneys was made (also through the capsules) with a very fine needle (No. 14 cambric, the size usually employed for closing the puncture in the aorta), which permitted a minute quantity of liquid from the blood-vessels to escape. By closely observing this liquid as it spread out on the capsule, the presence of red blood-corpuscles could be observed. It is doubtful whether in any instance such liquid was altogether free of such corpuscles. The perfusions, therefore, were relatively, and not absolutely, complete. The same was in general true for the anæmias, though the amount of arterial blood reaching the kidneys was small.

On releasing the temporarily occluded arteries, the kidneys rapidly assumed an appearance indicative of a very active circulation.

In the case of anæmia alone of the kidneys, or of the kidneys and suprarenals together, no abnormal symptoms were observed in the behaviour of the animal, and recovery was uneventful. When one kidney was subjected to anæmia alone, and the other to anæmia with perfusion the result was the same. Anatomically, the changes thus far observed have been less marked when perfusion was not practised.

In the case of Cat 22, in which one kidney was rendered anæmic, while the other was in addition perfused with Locke's solution, a marked increase in size of the former (compensatory hypertrophy ?) with practically complete disappearance of the latter (perfused) kidney was observed 155 days after the operation. Twelve months later the animal was photographed and then killed with chloroform, and the kidneys photographed (see p. 237).

No marked histological alterations have been observed. Eisendrath and Strauss, using rabbits, have confirmed the results as to absence of marked structural alterations in kidneys after short periods of anæmia; but they obtained no results as to the effect of such procedure upon the renal function, as they operated upon but one kidney. And as Wells pointed out in discussing their results, "cells may show extensive histological changes and be functionally competent; and may also show no histological changes, and be totally incompetent." Of great interest in this connection, is Wells's observation that fattily degenerated liver cells showed as great power to destroy uric acid, which is difficult to oxidize, as normal liver cells.

No chemical studies have been made when anæmia alone has been practised. The metabolism of such animals has suffered no marked alteration, as judged by the condition, behaviour, etc.

After anæmia with perfusion of the kidneys, cats as a rule show no unusual symptoms for twenty-four hours or more. During this time they appear the same as any cat on which a major surgical operation has been performed. In the more acute types of cases the usual symptoms of renal insufficiency rapidly develop, terminating in the death of the animal within a week or ten days, while in the slower types such pronounced symptoms do not appear for weeks or months. In all cases where such symptoms have been pronounced, death has invariably occurred within a few days. As a rule death follows the appearance of such symptoms more quickly in the acute than in the slower types of cases. In the latter especially, the animals usually showed great emaciation before death, or even before the onset of convulsive symptoms. With the onset of convulsions, in all cases death occurred within a few days. In the more acute cases the character and train of symptoms were practically indistinguishable from the symptoms following simple ligation of the renal blood-vessels or double nephrectomy. For a day or two preceding death there appeared to be a more or less complete suppression of urine. The pupils usually showed marked constriction during the period of slighter convulsions and during the onset of the stronger ones, but during the height of the stronger convulsions they became dilated. It may be remarked that such changes in the pupils are probably due to deficient respiration, it being known that partial asphyxiation produces a constriction, followed by a dilation, if the asphyxia be sufficiently complete.

As a rule, when examined up to a few weeks after the operation, the grosser anatomical changes consisted in what may be termed a "subnormal resiliency"—*i.e.*, the kidneys feel more or less flabby; in appearance they are pale; on section the cortex is pale, the medulla congested, and in the boundary zone a marked stripe of congestion is seen. The tissue has more or less of the "cooked" appearance that pathologists have associated with parenchymatous degeneration. Ultimately the kidney becomes harder, and on section less medullary congestion is seen. The cortex is paler than normal.

The most prominent histological feature in early examinations is the congestion. This is greatest in the boundary zone and medulla. Later, interstitial hæmorrhages occur throughout the entire organ.

At this stage cloudy swelling, of the tubular cells especially, is observed. This, and the succeeding degeneration, is also very marked in the cortex. Cellular infiltration also occurs, particularly in the boundary region. The degenerative process may proceed until cell structure is lost. As a rule such processes are more marked in certain areas than in others, so that such areas are surrounded by tissue showing more nearly normal structure. Such degeneration may result in the disappearance of Malpighian corpuscles as well as tubules proper.

Observation on chemical changes were confined to the urine.

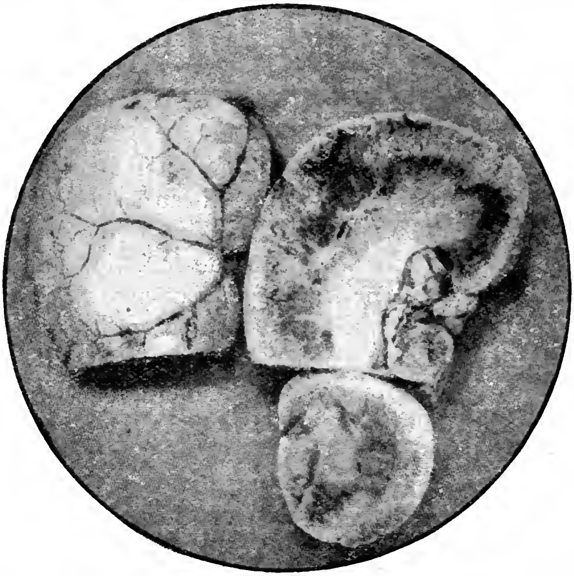


FIG. 110.—KIDNEYS OF CAT 32, WHICH WERE PERFUSED WITH SALT SOLUTION JANUARY 26.
The animal died February 15, twenty days after perfusion.
(*Archives of Internal Medicine*, 1910, v. 232.)

At first there seemed to be a decrease in the amount of urine. Such urine showed a high specific gravity and a high percentage of normal solids—*e.g.*, urea and chlorides. In the more protracted cases the amount and composition might approach the normal for a time, but prior to death another change occurred, so that the specific gravity and content of normal solids might sink below the normal. [It is interesting to note the composition of normal cat urine. The daily average for one of our control cats for one week was as follows: Amount, 91·4 c.c.; specific gravity, 1·059; chlorides,

abundant; urea, 17·5 per cent. by the hypobromite method. This figure for urea is unquestionably too high. For some reason the hypobromite method has indicated far too much urea in all cats' urines to which it has been applied.] Neither albumin or sugar have been observed, at least in sufficient quantities. Since the interpretation of such results is a matter requiring care, owing to the great complexity of factors—*e.g.*, amount and composition of the food eaten, liquids drunk, body weight, physiological state, etc.—a more complete discussion is not possible with present data. The metabolism appears to suffer great alterations, as judged not only by changes in the urine, but by loss of appetite and weight and change in general behaviour.

The results show conclusively that renal and adrenal anæmia, coupled with perfusion with all the solutions tried, is much more harmful than anæmia alone. Anæmia alone is certainly not to be looked on as being without effect, but it seems that for cats, under the conditions of these experiments, short periods of occlusion are not incompatible with permanent recovery of the animal. The observations have not been carried sufficiently far to enable us to conclude that the life of the animal is not shortened by the anæmia. Neither may we conclude that anæmia with perfusion as performed, invariably shortens the period of life remaining to the animal; for in few cases, when death did not occur for some months, we cannot be absolutely certain—though the evidence on the whole is strongly in this direction—that death was due to the operation. Carrel, in repeating Chirie and Mayer's work on the effect of temporary occlusion of the renal veins on dogs, observed death in one case in a few months after the operation, the period of occlusion being twelve minutes. He attributed death to *ostéo-périostite* of the atlas.* But it seems simpler to assume that the operation had a share in causing death, since Chirie and Mayer observed epileptiform manifestations and rapid death o dogs in which the renal veins had been occluded for ten minutes. As before indicated, the completeness of the anæmia during the period of occlusion is no doubt an important factor, and better control of this may tend to render the results of different investigators more uniform. In addition to this, however, differences in resistance to anæmia, as well as to anæmia with perfusion, will probably be demonstrated not only in animals of different species, but in individuals of the same species.

For the present, therefore, since all solutions seem to have a toxic

* Carre . *Comp. Rend. de la Soc. de Biol.*, 1909, lxvi. 527.

ABLE OF EXPERIMENTS ON ANÆMIA AND PERFUSION OF KIDNEYS.*

No.	Date operated.	Aorta occluded.		Period perfused.		Solution perfused with—	Death after (Days).	Remarks.
		Min.	Sec.	Min.	Sec.			
16	24/4/08	13	0	11	0	Ringer's	3	Both kidneys perfused.
17	25/4/08	13	0	11	0	Ringer's	9	Both kidneys perfused, nerves cut.
18	29/4/08	11	0	9	0	Ringer's	1	Both kidneys perfused, clot in aorta.
19	7/5/08	13	0	10	0	Ringer's	3	Right kidney *only* perfused.
20	7/5/08	14	0	8	30	Ringer's	2	Both kidneys perfused.
21	23/5/08	15	0	12	0	Locke's	3	Both kidneys perfused.
22	23/5/08	9	45	8	20	Locke's	364	Anæmia of both kidneys, right only perfused. Chloroformed.
23	23/5/08	12	30	0	0	0	40†	Anæmia only of kidneys. Escaped in July in good condition. Showed no symptoms of renal insufficiency.
24	3/11/08	22	0	0	0	0	8†	Anæmia only of kidneys. Cat in splendid condition until eighth day, when abdominal wound opened owing to absorption of gut suture material, allowing the intestines to escape.
25	3/11/08	0	0	0	0	0	2·5	Ligated renal vessels permanently.
26	3/11/08	0	0	0	0	0	6	Excised kidneys.
29	16/12/08	20	35	7	0	0·9 NaCl	84	Partial perfusion only of both kidneys.
30	16/12/08	28	0	16	30	Starch	1·5	Both kidneys perfused.
31	22/12/08	16	0	8	0	0·9 NaCl	131	Left kidney excised.
32	26/1/09	25	0	15	30	0·9 NaCl	20†	Clot in aorta. Some temporary paralysis. Chloroformed after recovery.
33	26/1/09	9	0	4	15	0·9 NaCl	123†	Partial perfusion both kidneys.
34	26/1/09	16	30	12	30	0·9 NaCl	105†	Both kidneys and adrenals.
35	26/1/09	14	10	10	0	Locke's	7	Both kidneys and one adrenal perfused.
36	27/1/09	10	0	2	15	0·9 NaCl	474	Partial perfusion both kidneys.
37	27/1/09	12	30	5	0	0·9 NaCl	101	Partial perfusion both kidneys and suprarenals.
38	27/1/09	10	30	7	0	Locke's	683 (about)	Right kidney removed. Had several litters of kittens. Always very thin, finally became very sick and disappeared.
39	27/1/09	9	0	5	30	Ringer's	36	Both kidneys perfused.
40	27/1/09	11	30	5	30	Ringer's	33	Both kidneys perfused.
41	27/1/09	14	15	9	30	Locke's	32	Both kidneys and adrenals perfused.
42	4/2/09	18	0	12	0	0·9 NaCl	7	Both kidneys and right adrenal perfused.
44	4/2/09	19	30	12	0	0·9 NaCl	14	Both kidneys perfused. Young cat.

* *Journal of the American Medical Association*, 1908, li. 1658, and *Archives of Internal Medicine*, 1910, v. 232.

† Indicates that the animal escaped or was killed. This is usually indicated under "Remarks." Nos. 33 and 34 are exceptions. They were chloroformed after they became too weak to stand. The amount of liquid perfused varied from about 10 to 30 c.c., in general the amount varying with the period of perfusion. In no case, with the possible exception of Cat 30, was the perfusion made with the pressure exceeding an average blood-pressure in cats. The solutions were brought to body temperature before beginning the perfusions in most cases, but when the room was very cold the temperature of the solution was considerably lowered before it entered the blood-vessels. The following temperatures were recorded: For No. 30, 15°; No. 31, 37°; No. 36, 30°; No. 38, 15°; No. 39, 20°; and No. 41, 12° C. These temperatures were taken by allowing the liquid to spurt through the needle on to the bulb of a thermometer.

action, it would be unprofitable to discuss the apparent small differences in the toxicity of the solutions used on the cats (see p. 120).

Borst and Enderlen claim to have observed a dog to live one hundred days or more after one of its own kidneys had been removed and replaced in the abdominal cavity with vascular and ureteral anastomosis, with removal of its other kidney.

No one has as yet reported successful results in transplanting kidneys from one individual to another, even when very closely related individuals have been used, for more than a few weeks ; and no one has succeeded in keeping an animal alive with the kidney or kidneys from an animal of a different species for more than a few days. When it is remembered that an animal may survive for a period of ten days or more after removal of its kidneys, the fact that an animal may survive a few days when its own kidneys have been removed and replaced with kidneys from another animal does not indicate that such engrafted kidneys are performing an adequate renal function. Of course, when an animal is permitted to retain one of its own kidneys after such an operation, the fact that it may survive for weeks indicates nothing as regards the functional state of the foreign kidney; for an animal may get along very well indeed with but one of its own kidneys.

Therefore, the only results that speak for a degree of functional activity of engrafted tissues are those observed in animals surviving for weeks after all of their normal renal tissue was removed. From this standpoint it may be concluded from results hitherto reported that a re-engrafted kidney or kidneys may adequately functionate to preserve the life of the animal at least for months. Also it may be concluded that a foreign kidney, even though it be from a very closely related animal of the same species, can only functionate adequately to preserve the life of the animal for at the most a few weeks.

Most investigators agree that an engrafted foreign kidney or kidneys from a different species has not shown evidence of prolonging the life of the host ; but since it is now known that the perfusion that has been practised in transplantations is of itself harmful, and since it is known that it is possible to perform the operation so quickly as to render such perfusion for the purpose of preventing intravascular coagulation unnecessary, we may confidently hope for more uniform and permanent results in cases of auto-engrafted kidneys. But from such results only experi-

mental and therefore only indirectly practical benefits may be derived, for auto-renal grafts will, for obvious reasons, never be of direct practical importance; for if the operation is ever applied therapeutically, it will be for the reason that the animal's own renal tissue is deficient or abnormal, and for that reason the operation will be performed with the view of engrafting renal tissue from another animal. Here, again, the obstacle of inadequate survival or adaptation of such engrafted renal tissue is encountered. The outlook is by no means hopeless, but it would not be practicable to enter into a discussion of the probable reasons, or the methods that might be tried experimentally with the view of overcoming the difficulty other than to say that the principles of immunity, which yield such brilliant results in many other fields, would seem to be worthy of being tested in this case.

Results of Transplantation of Thyroid.

For a long time it has been known that thyroid tissues may be successfully engrafted. Schiff and Kocher, in the early eighties, the former using dogs and the latter operating on man, obtained temporary benefit by engrafting after removal of the thyroids. In 1892 Eiselberg reported anatomically and physiologically successful results on cats. A little later Cristiani reported successful results on numerous species of animals. All such transplantations have been performed without anastomosis of the blood-vessels, so that the results have been best when thin masses of tissues have been employed.

With Carrel, in 1905, one thyroid lobe of a dog was removed, and after washing out its vessels with salt solution it was replaced in the situation from which it was taken, and the circulation through it restored by anastomosing the peripheral end of the superior thyroid vein to the central end of the corresponding artery, and the peripheral end of the artery to the central end of the vein, thus establishing a reversed circulation through these vessels. Great swelling of the gland occurred, and some infection ensued, but the swelling soon disappeared and the wound healed. The dog never showed any general symptoms indicative of deranged thyroid metabolism. Two years and nine months later the animal, which was retained by the writer, was killed with chloroform and the specimen examined.

Anatomically, the left thyroid lobe was moderately enlarged and presented the appearance of colloidal goitre. The right lobe was

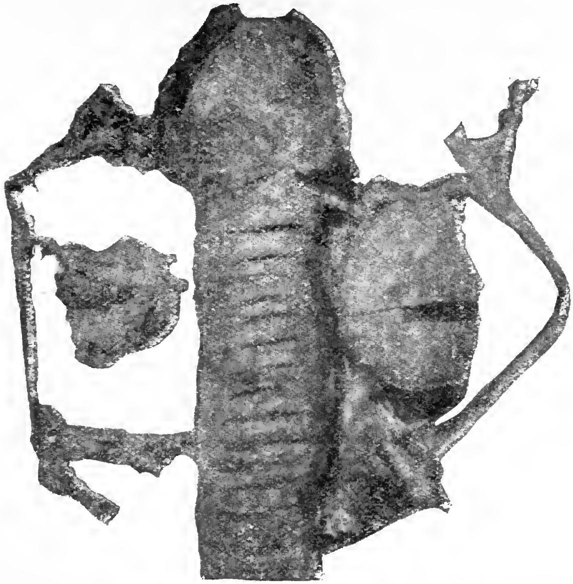
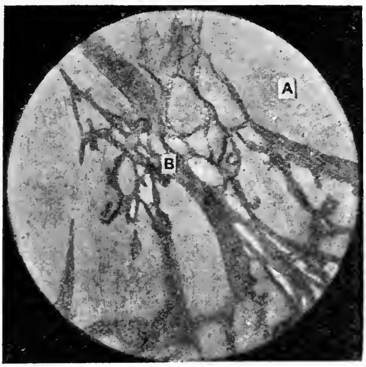


FIG. 111.—RIGHT THYROID LOBE OF DOG, THIRTY-THREE MONTHS AFTER REMOVAL AND REPLACEMENT, WITH REVERSAL OF CIRCULATION IN SUPERIOR THYROID ARTERY AND VEIN.

(*Journal of the American Medical Association,* 1910, liv. 831.)

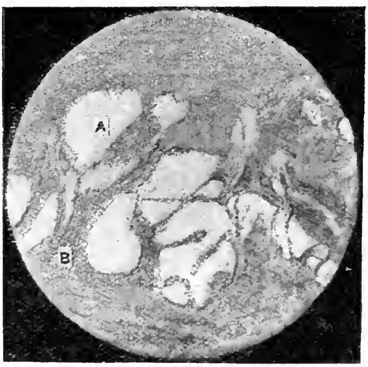


UNOPERATED.

FIG. 112.—MICROPHOTOGRAPH THYROID LOBE (DOG 00), NOT OPERATED ON.

Note large amount of granular colloid (A) and small amount of clear colloid (B), and fibrous relations.

(*Journal of the American Medical Association,* 1910, liv. 831.)



REPLANTED

FIG. 113.—MICROPHOTOGRAPH THYROID LOBE (DOG 00), OPERATED ON.

Note clear colloid (A) and enormous amount of fibrous tissue (B). No granular colloid.

(*Journal of the American Medical Association,* 1910, liv. 831.)

quite fibrous and dense to the touch and adherent to surrounding structures. On dissection, the superior thyroid vessels were found intact. Owing to the fibrous adhesions it was difficult to make a satisfactory dissection of the vein. The artery and the point of union of artery to vein is shown in the illustration.

Microscopically, the lobe which had not been operated on presented the appearance of colloidal goitre. The lobe which had been operated on showed an enormously thickened connective tissue capsule. The substance of the gland showed an abundance

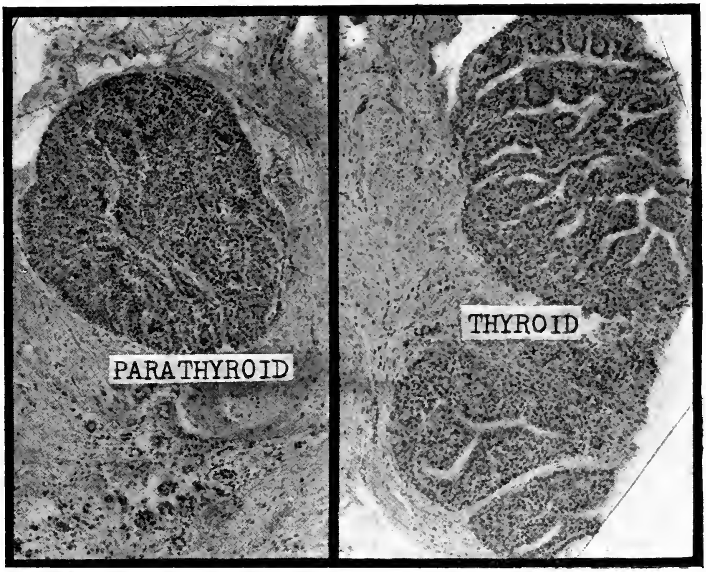


Fig. 114.—Autograft from Dog, excised at the Operation of Functional Test, Four Months after its Transplantation. Enlarged $\frac{90}{1}$ (Halsted.)

Death from tetania parathyropriva promptly followed its excision.

(*Journal of Experimental Medicine*, 1909, xi. 175.)

of normal staining colloid. The walls of the acini were considerably thicker than normal, due in part to strands of connective tissue. Otherwise the histologic elements themselves appeared normal, the arrangement only being abnormal. Capelle (p. 16) reports a result indicating functional as well as anatomical survival of a thyroid re-engrafted into a dog's neck. Two hundred and forty-five days after the operation the gland was removed and the dog died in typical post-thyroidectomy tetany.

Results of Transplantation of Parathyroids.

The results of parathyroid transplantations by vascular anastomoses have not been sufficiently studied to consider at this time. Recently, however, Halsted has reported completely successful parathyroid grafting by the simple method.

His results indicate that the survival of an exceedingly small fragment of such tissue seems adequate to prevent the appearance of the symptoms of thyro-parathyroidectomy (tetany, etc.). For example, after transplanting two parathyroid bodies and removing the remainder of the thyroid tissues, the dog remained in good health. Some months later but one of the engrafted parathyroid bodies could be found. This was removed and preserved. "The dog died of tetania parathyropriva on the second (or third ?) day after the operation," thus proving the functional state of the removed autograft. The tissue was microscopically examined, and the results are shown in Fig. 114.

Results of Transplantation of the Heart.

The heart of a small dog was extirpated and transplanted into the neck of a larger one by anastomosing the cut ends of the jugular vein and the carotid artery to the aorta, the pulmonary artery, one of the vena cava, and a pulmonary vein. The circulation was re-established through the heart, about an hour and fifteen minutes after the cessation of the beat ; twenty minutes after the re-establishment of the circulation the blood was actively circulating through the coronary system. A small opening being made through the wall of a small branch of the coronary vein, an abundant dark hæmorrhage was produced. Then strong fibrillar contractions were seen. Afterward contractions of the auricles appeared, and about an hour after the operation effective contractions of the ventricles began. The transplanted heart beat at the rate of 88 per minute, while the rate of the normal heart was 130 per minute. A little later tracings were taken. Coagulation occurred in the cavities of the heart after about two hours, and the experiment was interrupted.*

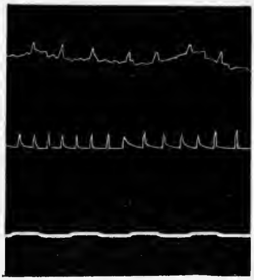


Fig. 115.—Record of Contractions of Engrafted Heart (Upper Tracing) and of Animal's own Heart (Middle Tracing).

The lower tracing shows time.

* The experiment is quoted from a paper by Carrel and the writer in *American Medicine*, December 30, 1905, vol. x., No. 27, pp. 1101-1102.

Transplantation of the Lungs and Heart.

"We attempted also the transplantation of the lungs together with the heart. Both lungs, the aorta, and vena cava of a cat one week old were extirpated and put into the neck of a large adult cat. The aorta was anastomosed to the peripheral end of the carotid, and the vena cava to the peripheral end of the jugular vein. The coronary circulation was immediately re-established and the auricles began to beat. The lungs became red, and the ventricle began to contract strongly; but œdema of the lungs soon appeared and the right heart became distended. Owing to infection the examination was discontinued two days later."*

Results of Transplantation of the Head.

May 21, 1908.—Moderate-sized dogs used.

2.35 p.m.: Etherized.

3.18: Head to be engrafted was amputated.

3.25: Common carotid artery of right side of host was anastomosed to same vessel on left side of engrafted head.

3.36: External jugular vein similarly anastomosed.

3.47: Circulation restored; period of anæmia in engrafted head was twenty-nine minutes.

4.18: Operation completed (muscles, skin, etc., sutured); ether removed. The following observations refer to the engrafted head:

4.30: First movement of nostrils noticed, indicating respiratory discharge; tongue twitching; colour of tongue is pink.

4.31: Respiratory movements about 2 per minute.

4.32: Pupils contracting.

4.37: Respiratory movements continue at intervals of about eleven seconds.

4.39: Muscles of the throat contract with respiratory effort.

4.46: Lids closed; pupils contracted; respiratory movements continue; tip of nose moist; tongue and mucous membrane red.

4.50: Gasping movements.

4.57: Muco-sanguineous fluid is discharged from nostrils; pupils very small.

5.12: Respiratory movements 10 per minute; respiratory rate of host 60 per minute.

5.17: Copious flow of saliva; none in host.

* *Johns Hopkins Hospital Bulletin*, 1907, xviii. 25.

5.27 : Pupils contracted ; fibrillary twitching of tongue, which is retracted completely ; jaws close when not restrained ; respiratory movements stronger, and rate 14 per minute.

5.31 : Secretion of tears and copious salivation.

5.45 : Temperature of both heads is 38° C.

6.00 : Pupils less contracted.

6.03 : Slight secretion of saliva from host.

6.37 : Respiratory rate of host 30 per minute ; respiratory rate of engrafted head 24 per minute ; respiratory movements are more gentle in character ; right pupil has been dilated a short time, while left pupil has remained well contracted. Saliva still flowing ; tongue not so greatly retracted, and fibrillary contractions less active than before.

6.55 : Pupils as before ; respiratory movements of nostrils have disappeared ; " boiling movement " of tongue.

7.00 : Respiratory rate of host 27 per minute, and deep.

7.05 : Circulation in engrafted head very active ; no movements observed, but saliva is still flowing.

8.35 : Temperature of both heads is 36° C. ; both pupils now dilated ; circulation remains good.

8.50 : Respiration in host 16 per minute ; physical conditions good.

9.40 : Respiration in host 14 per minute ; pulse 178.

9.50 : Drank water.

3.07 a.m. : Drank water ; respiration $18\frac{1}{2}$ per minute ; pulse 147 ; animal seems more animated.

6.28 : Circulation good in engrafted head ; respiration in host 21 per minute ; pulse 132.

8.23 : Vomited some pale greenish fluid.

9.40 : Respiration becoming laboured.

10.02 : Respiration more laboured ; etherized animal.

10.08 : Opened neck ; soft clot was found in the vein, which disappeared on slight manipulation ; arterial pulse good ; wound good ; only small amount of serous fluid escaped.

10.26 : Muscles of engrafted tongue and neck contracted when stimulated directly with induced current ; tongue shows " boiling movement."

Etherized animal.

May 27, 1908.—Two animals of same size were taken ; weight of host was 14 pounds.

Central ends of the carotid arteries and the central ends of the

internal jugular veins were anastomosed to the peripheral ends of corresponding vessels of the head to be engrafted. This was done before removing head.

3.21 p.m.: Neck and spinal cord severed. Began sewing muscles and skin of transplanted head to skin and muscles of host.

The following observations refer to the transplanted head:

3.22: Gasping movements, with twitching about mouth.

3.27: Gasping movements, with strong retraction of tongue. Respiratory efforts; eye reflex absent.

3.32: Operation completed; engrafted head quiet; anæsthetic discontinued.

3.49: Respiratory efforts again begin in head; pupils diminishing in size.

4-5: Animal demonstrated at a meeting of physicians and surgeons.

During this period the engrafted head gave evidence of aural, visual, and cutaneous reflex movements.

5.42: Pupils small; lid reflex good; makes respiratory efforts and gasps; no salivation.

6.13: Lid reflex good; pupils dilated; mouth dry.

6.27: Lid reflex absent; respiratory movements absent; circulation excellent.

6.40: Animal etherized; clamped arteries to engrafted head. This was followed by fibrillary twitching of the tongue and contraction of the muscles of the neck; also gasping movements. Animal killed, as the operation was not performed aseptically.

Results of transplantation of the head have been discussed in a preceding chapter (p. 116).

Transplantation of Blood (Transfusion).

It is known that when blood escapes from the vessels into the extravascular spaces that the red cells soon perish and are absorbed. Less is known of the fate of the white cells. But it would not be surprising if certain of them survive, for they are normally found in certain situations outside the blood. It seems probable that they largely re-enter the vessels without great change. So the introduction of blood into the extravascular tissues theoretically might be successfully employed for engrafting certain constituents of the blood. But such a method does not hold out even the theoretical possibility of success for the engrafting of the erythrocytes, not only for the reason mentioned, but Huber, in studying

the fate of extravascularly injected blood in anæmia, found that the red cells remain at the point of injection and retained largely their normal shape and staining properties for some days. He considers that the hæmoglobin eventually lakes out and enters the blood-vessels, thus aiding indirectly in restoring the patient's blood. In order, therefore, for transplanted red cells to have a chance to survive, it would seem to be necessary to introduce them into the blood-vessels (*cf.* p. 264). And as this has been done in transfusions, the subject will be considered from that standpoint.

By the term "transfusion" is meant the transference of blood from the vessels of one animal into the vessels of another. The operation is very old, and is one of the most interesting subjects in the history of medicine.

An interesting account was written by Howe in 1889. His article is freely drawn upon in the following pages.

Transfusion was performed in ancient times, but in a very crude way. Ovid, in his "Metamorphoses," gives an account of its performance by the sorceress Medea, who took blood from young healthy men, mixed it with vegetable juices, and injected it into the veins of old men who longed to renew their youth.

Savonarola, the celebrated Florentine monk, gives an account of the transfusion of Pope Innocent VII. The Pope had reached the average of life, and was suffering from a disorder which produced coma. Two young men in good health were obtained who were willing to give their blood to save the Pontiff. The patient was bled, and the blood which escaped was injected into the veins of the young donors. When the blood had circulated a short time the young men were bled, and the blood was transferred to the veins of the Pontiff. The operation proved fatal to both patient and donors.

In 1615 Libavius advocated arterial transfusion by means of silver tubes passing from a blood-vessel of the donor to one of the recipient.

In 1665 Lower of Oxford performed the operation with success. He bled animals to a condition of syncope, and then resuscitated them by injections of blood from other animals.

Denys of Paris followed Lower in these experiments. He transfused a patient who had been bled and purged for fever. Ten ounces of lamb's blood were injected, and the patient recovered. Subsequently he was called to an insane patient who had been bled and purged without changing the irregular current of his thoughts.

He injected nine ounces of calf's blood, and recovery from the mental disturbance was the result. Three months later the mental trouble returned, and Denys attempted to operate again, but on opening the vein in the patient's arm found that no blood flowed. He did not finish the operation, and the patient died. The wife charged the physician with killing her husband, and the latter retaliated by saying that she had administered poison to him. The case created considerable excitement in Paris, the operation fell into discredit, and a law was finally passed forbidding its performance unless the consent of all the faculty had previously been obtained. As a matter of course, this order was tantamount to a complete prohibition, and transfusion in France was for a time abandoned.

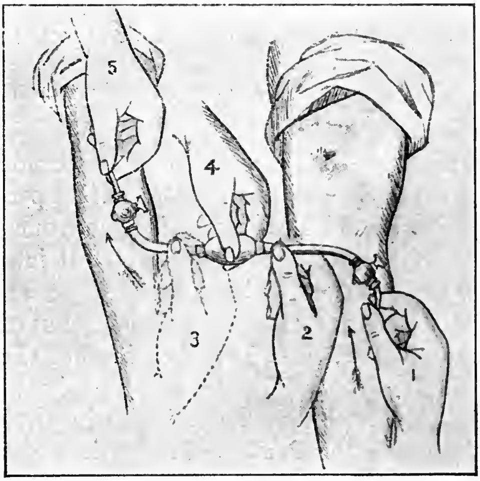


Fig. 116.—Aveling's Transfusion Apparatus.

1, 5, Hands of the assistant holding the cannulæ in position; 4, hand of the operator compressing the bulb; 2, 3, hand of the operator compressing alternately the afferent and efferent tubes.

In 1665 two German surgeons, named Kaufmann and Purmann, claimed to have cured a leper by the repeated injections of lamb's blood. Dr. Schmidt, of Damrech, injected medical agents as well as blood with a certain degree of success in exhausting diseases and after hæmorrhage.

In 1667 Mayer, another German surgeon, performed the operation of transfusion.

In 1825 Dr. James Blundell, of London, gave to the operation a new impetus. He operated upon dogs, first bleeding the animals until pulse and respiration ceased, and then injecting fresh blood. He established conclusively the already half-proved fact that animals apparently dead could be resuscitated by transfusion at the end of three or four minutes, but that if the operation were delayed for more than five minutes it proved of no avail. Dr. Blundell also tried injections of blood in dogs that had been kept without food for two or three weeks. After three weeks had elapsed he found that the blood failed to sustain the animal.

His first experiments upon men were not as successful as his experiments upon animals. Five successive failures resulted, probably because the operations were performed at too late a period. Subsequently, however, he was more successful, and thereby gave to the operation a character which it never had before.

Edmund King, Thomas Coxe, and Russel of Suffolk also practised transfusion successfully.

Surgeons have differed in regard to the utility of taking blood from one animal and injecting it into another of a different species. In 1755 Michael Rosa, of Oden, made a number of experiments, and came to the conclusion that an exsanguinated animal might be resuscitated by the injection of blood from an animal of a different species. Russel of Suffolk is said to have cured a case of hydrophobia by opening the veins of the patient, allowing some blood to flow, and then transfusing the blood from several lambs. Blundell satisfied himself that the blood of a dog would resuscitate a dog, but that the blood taken from a human biped had no beneficial effect whatever. Laing believed that the blood of calves and other animals contained particles of various kinds necessary for the development of such peculiar tissues as horn, etc., belonging to these animals, and that, consequently, these elements would prove deleterious when in the vascular system of the human patient. In 1889 there was scarcely any difference of opinion with regard to the use of blood from lower animals, it being regarded as dangerous, and was seldom or never employed. And now, more than twenty years later, the same opinion prevails.

Another question which had received much attention prior to 1889 was as to the value of defibrinated blood. Many believed that the fibrin of the blood possessed qualities of a poisonous nature, which made it useless as a factor in restoring lost vitality, and that therefore this element should be removed by whipping and straining before the fluid was injected into the veins of the patient. Others believed in defibrinating the blood in order to remove the danger of coagulation in the venous capillaries of the lungs. Magendie and Bernard, on the other hand, considered that the fibrin assisted capillary circulation, and that by it the blood was enabled to traverse the capillaries in a much more viscid stream. Panum of Copenhagen considered that no immediate or special nutritious effect would result from transfusing defibrinated blood.

Howe claimed to have used both defibrinated and undefibrinated

blood successfully; but he considered it much better to inject the blood without going through the process of defibrinating it. In the first place, he pointed out that whipping the blood makes it possible for poisonous germs to enter the liquid. If the whipping was performed in the wards or amphitheatre of a hospital, the entrance of germs into the circulation could hardly be prevented. (But this objection should not be valid now.) In the second place, the mass of fibrin taken from the blood carries off with it a large number of globular elements entangled in the meshes, which must necessarily lessen the restorative qualities of the blood. If defibrination can be dispensed with, wrote Howe, so much the better. For fifteen years prior to 1889 he used undefibrinated blood without any unpleasant results. In a few cases the blood was injected as it flowed from the veins, but in the larger number he used a solution of carbonate of ammonia (10 grains to the ounce), adding 2 ounces of this to the blood before transfusing. This was done in order to remove the possibility of the formation of clots in the veins, and also the stimulating effects of the ammonia was held to be valuable in many cases.

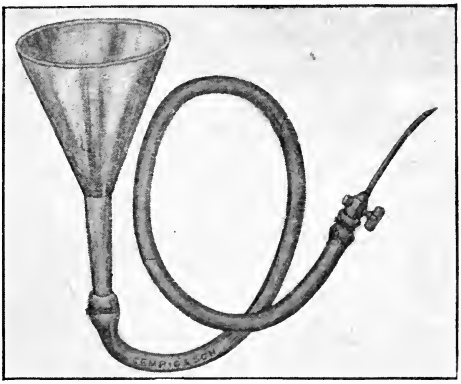


FIG. 117.—GLASS FUNNEL AND TUBE EMPLOYED IN TRANSFUSION. (HOWE.)

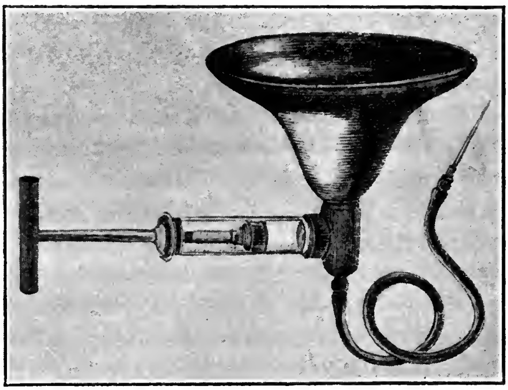


FIG. 118.—COLIN'S TRANSFUSION APPARATUS.

Howe mentioned five varieties of transfusion: immediate, mediate, peritoneal, auto-transfusion, and injection of blood into the cellular

tissue. Although he considered that transfusion in the strictest sense meant only the introduction of blood into the blood-vessels, he said that "in immediate transfusion the blood is transferred directly from the donor to the patient by means of connecting silver tubes or by the aspirator."

"In mediate transfusion the blood pours from the donor's arm into the basin of the instrument prepared to receive it, and is afterwards injected (with or without defibrination) into the veins or arteries of the patient.

"Peritoneal transfusion consists in the injection of blood into the cavity of the peritoneum.

"Auto-transfusion can scarcely be called an operation, but it is often of value in keeping up the supply of blood to the nerve-centres. It consists in bandaging the limbs of the patient, and thus forcing the blood to the central organs.

"Injection of blood into the areolar tissue is performed with a large hypodermic syringe. It is seldom employed."

The nutritions and stimulating fluids employed in transfusion were: first, blood defibrinated and undefibrinated; second, milk from the cow, goat, or human mammary glands; and third, saline solutions.

The indications for the operation of transfusion were: excessive hæmorrhage; malignant syphilis; chronic or pernicious anæmia; prolonged suppuration; scurvy or purpura hæmorrhagica; carcinoma; blood-poisoning from carbolic acid, illuminating gas, etc.; and white softening of the brain or cord.

In describing the methods, Howe said that "when special instruments are not at hand for the performance of the operation, an ordinary rubber or glass syringe may be used. If it is considered necessary to defibrinate the blood, the best basin for the purpose is a china or glass finger-bowl. The most prominent vein in the patient's arm should be selected—either the median basilic or the median cephalic, it matters little which. After stirring the blood vigorously, large clots form and are removed, and then the additional precaution is taken of straining the blood through a piece of muslin into another finger-bowl prepared for the purpose.

"The bowl of blood thus prepared is then placed in a basin containing water at 110° F., and allowed to remain there until an opening is made in the cephalic vein or in any other vein in the arm which is easy of access. The blood is then injected with an ordinary rubber or glass syringe, or allowed to flow from an ordinary glass

funnel connected with the vein by a rubber tube and cannula. The glass funnel, however, is much better suited for the transfusion of milk than for the transfusion of blood.

"When the operator has nothing but a syringe to perform the operation with, he will find that a small goose-quill is very useful as a cannula. The blood can be injected through it with ease.

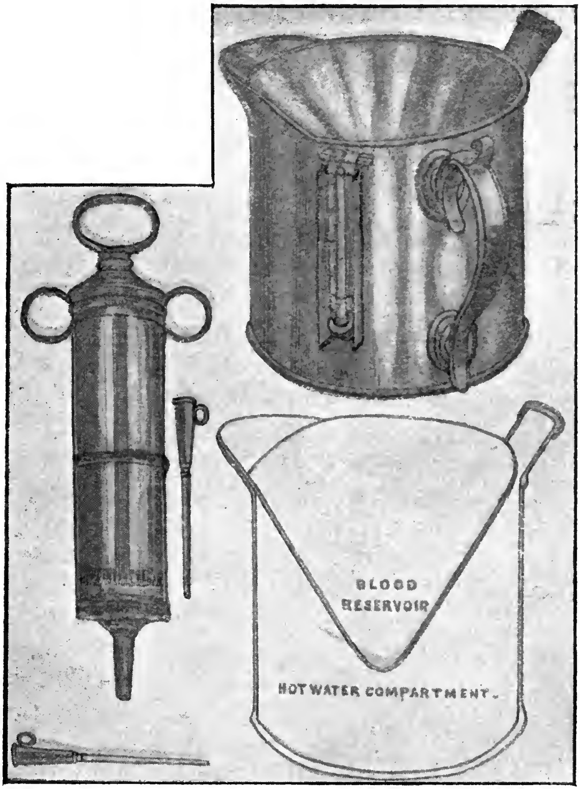


Fig. 119.—Morton's Transfusion Apparatus.

"As a rule, the vein selected for transfusion is the cephalic vein. If that is not accessible, any other vein, even in exsanguinated patients, may generally be seen as a faint blue line under the integument on the outer and anterior aspect of the arm. In patients who are very fat this vein may not be visible. In such cases the median cephalic or median basilic may be opened. When the cephalic vein is not perceptible, a little pressure upon it for a few minutes will

suffice to bring it into view. When the position of the vein has been determined, the integument over the vein is to be pinched up with the thumb and forefinger and incised with a bistoury or scalpel; the fingers then being removed, the elastic skin retracts on each side, exposing the fine delicate blue line of vein embedded in the cellular tissue beneath. A few scratches with the scalpel on each side of the vein exposes it more and separates it thoroughly from

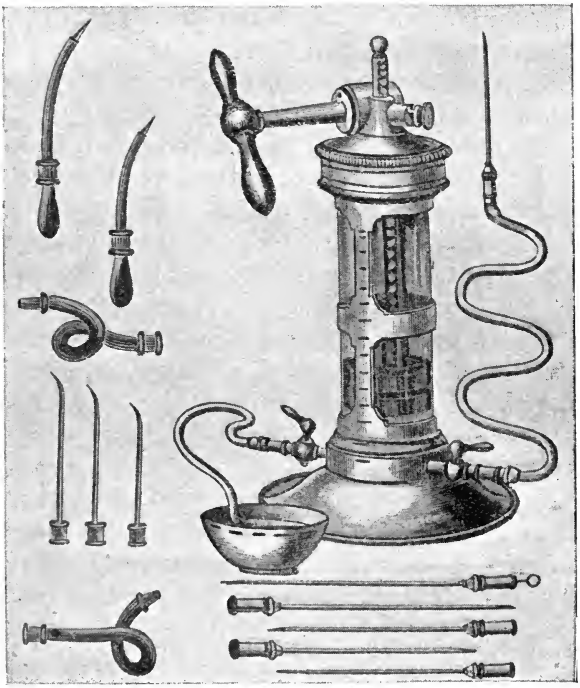


FIG. 120.—DIEULAFOY'S ASPIRATOR, PREPARED FOR USE IN TRANSFUSION.

the cellular tissue, making it easy to pass a director underneath and lift it above the level of the integument.

"Some surgeons, before opening the vein, place a ligature around it below the point of opening in order to prevent the escape of blood, but this is altogether an unnecessary procedure. The fingers of an assistant answer the purpose equally as well, and less injury is done to the vein.

"The vein is now pinched up from the director by means of dressing forceps, and is carefully opened by a few transverse

scratches with a scalpel. The cannula is inserted and retained by the fingers of an assistant, who holds it in position during the whole of the operation."

To draw blood from the donor, he says :

"A roller bandage 2 or 3 inches wide is placed around the arm near the elbow, and tightened sufficiently to obstruct the circulation through the veins without interfering with the arterial current. A piece of wood or other hard substance is then firmly grasped by the patient with the forearm flexed, so as to increase the distension of the superficial veins.

"The median basilic or the median cephalic may now be opened, and the blood allowed to flow into any basin or vessel that the operator may have selected. An opening $\frac{1}{2}$ inch in length will cause a free flow of blood and lessen the tendency to coagulation.

"While the patient is being subjected to the operation of transfusion, various symptoms may arise which it will be well to understand. After the first ounce or two of blood has entered the circulation, the patient may complain of vertigo and dimness of vision. In such a case a few moments should be allowed to elapse before another syringeful is injected. The patient may also complain of a constriction of the chest and some slight difficulty in breathing. Here, again, the operation should be suspended until these symptoms are removed.

"There are also in some cases coma, pains in the loins, and often a very severe pain in the lumbar region. The patient may complain of prickly sensations in the extremities, especially when the operation is approaching completion. In all cases it is well for the operator to stop and ask questions before the next syringeful is used. If the patient is unable to speak, he will always get a negative or affirmative movement, which is all that is necessary. It is not necessary to transfuse more than 7 or 8 ounces of blood, and 4 or 5 ounces will often save a life. Some cases are on record in which the patient was restored by an ounce or two. While that amount would doubtless be productive of some little benefit, it would not suffice to save a patient who had been bled to a state of syncope either by accident or design.

"Following the operation there is also a train of peculiar symptoms. As a rule, if the patient is going to revive, the pulse and voice will be restored together. Usually within an hour the patient has a well-marked chill, followed by a febrile movement which lasts some hours, the temperature rising from 1° to 3° F. The rise in

temperature is greater when the operation is performed in phthisical cases than in any others.

"The other febrile symptoms, such as headache, pains in the loins, thirst, etc., are also present to a greater or less degree. The flow of urine is sometimes increased, and it may contain albumin. In some, it becomes scanty and high-coloured, especially when the temperature has been much increased by the operation. In some cases coma occurs.

"Transfusion of blood is commonly considered a dangerous operation, especially by those who have never performed it. But although the operation is generally made on a pulseless and moribund patient, a death occurring during or from the operation is of very rare occurrence, which is a sufficient evidence that this opinion is not well grounded. The dangers from the formation of coagulation in the veins and from the entrance of air are almost impossible with the instruments in present use [1889]. In any event, all that is necessary for success is to inject the blood slowly, carefully watching its effects.

"The first and foremost indication for the performance of transfusion is excessive loss of blood. Whenever the physician is called to an exsanguinated patient, where the pulse is absent or scarcely perceptible, with sighing and irregular respirations, a face of ghastly pallor, extremities cold and clammy, with all the signs of rapidly approaching dissolution, he has a typical case for transfusion."

An interesting case, ultimately making a complete recovery, occurred among Howe's early operations of transfusion. The patient had had a miscarriage two weeks before, and profuse hæmorrhage every day since. Her physicians had been in close attendance night and day, doing everything in their power to keep her alive.

"I saw her at 7 a.m. She had all the symptoms of loss of blood previously enumerated, but in addition she was insensible and evidently dying. As there was no time to lose, I injected 7 ounces of undefibrinated blood, unmixed with ammonia, by means of Colin's instrument. In a few minutes afterwards the patient articulated without any difficulty, her pulse returned at the wrist, she swallowed a little beef-tea, and kept on gradually from that time gaining strength until complete recovery took place."

Dr. T. G. Morton, of Philadelphia, prior to 1889, employed transfusion in three cases of purpura hæmorrhagica with success. "The first case was a child, eleven years of age. She had three attacks

of purpura, with bleeding from the nose. She had never during these attacks been alarmingly ill, but early in 1874 she was suddenly seized with hæmorrhage from the nasal mucous membrane. The skin from head to foot presented the usual characteristic spots, some of which were of enormous size. When she was nearly exhausted, transfusion was performed as a *dernier ressort*, with a happy result." Howe says: "Some two months afterwards a recurrence of hæmorrhage with all the former symptoms obliged me to transfuse again, for an immense amount of blood had been lost before I saw the case. The very rapid recovery which took place after both these operations presented a marked contrast with the tardy convalescence following the previous attacks, which, although much less severe in the amount of blood lost, had confined the patient to bed for many months. Three years have elapsed since the transfusion, and during this period she has had but one attack of nasal bleeding, which was early controlled by plugging."

Howe stated that "such cases as these may be found recorded year after year in medical journals on both sides of the Atlantic, and it seems as if no further evidence could be needed to show the efficiency as well as the necessity of resorting to transfusion in all cases of hæmorrhage without delay."

From this perhaps too lengthy account, it is clear that the conception, methods, practice, and application of transfusion and injection of blood in the lower animals and man are not new, and that many and careful clinical observations and experimental studies were made generations ago. And it is further interesting to note that current views upon the subject, especially as to the clinical applications and limitations, do not differ essentially from such views held for a quarter of a century or longer.

An account of some interesting transfusion experiments in rabbits performed for a very interesting reason is given by Romanes. Mr. Francis Galton, in the course of an experimental investigation of the truth of Darwin's theory of pangenesis, transfused the blood of one variety of rabbit into the veins of both sexes of another, and then allowed the latter to breed together. (It will be recalled that Darwin's theory of pangenesis is that all the units of the body, besides having the universally admitted power of growing by self-division, throw off minute gemmules, which are dispersed through the system. Further, that the gemmules multiply and aggregate into buds and constitute the sexual elements, their

development depending on their union with other nascent cells or units. Also, that they are capable of transmission in a dormant state to successive generations.)

In no case was there any appearance in the progeny of the rabbits of characters distinctive of the variety from which the transfused blood was derived. But, as Mr. Galton himself subsequently allowed, this negative result constitutes no disproof of pangenesis, seeing that only a portion of the parents' blood was replaced; that this portion, even if charged with "gemmules," would contain but a very small number of these hypothetical bodies, compared with those contained in all the tissues of the parents; and that even this small proportional number would presumably be overwhelmed by those contained in blood newly made by the parents. Nevertheless, the experiment was unquestionably worth trying, on the chance of its yielding a positive result. For in this event, the question at issue would have been closed. Therefore Romanes, with the aid of Professor Schäfer, repeated the experiments, but with slight differences in the method, designed to give pangenesis a better chance, so to speak.

He chose wild rabbits to supply the blood, and Himalayan to receive it. The former is the ancestral type (and therefore gives reversion an opportunity of coming into play), while the latter, although a product of domestication, is a remarkably constant variety, and one which differs very much in size and colour from the parent species. Again, instead of a single transfusion, several transfusions were performed at different times. Moreover, they did not merely allow the blood of one rabbit to flow into the veins of the other (whereby little more than half the blood could be substituted), but sacrificed three wild rabbits for refilling the vascular system of each tame one on each occasion. Even thus performed, however, the experiment yielded only negative results.

Subsequently Romanes decided that all this labour, both on Mr. Galton's part and his own, was simply thrown away; not because it yielded only negative results, but because it did not serve as a crucial experiment at all. For the material chosen was unserviceable for the purpose, inasmuch as rabbits, he became convinced, never throw intermediate characters, even when crossed in the ordinary way (*cf.* p. 287).

From these experiments it seems clear that large amounts of blood may be safely transfused between rabbits.

Hektoen and Carlson, in a study of the distribution of antibodies

and their formation by the blood, obtained very interesting results not only on the specific problem investigated, but also upon the question of transfusion of blood after severe hæmorrhage from one animal to another of the same species. Dogs were employed.

Large dogs were selected as donors and small dogs as recipients. A simple glass T-cannula was employed, as it was found that it could be used safely without clotting, and, compared to more

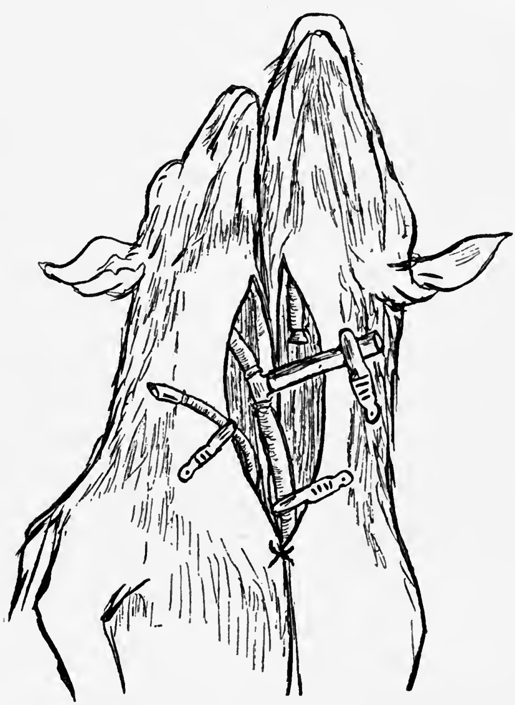


Fig. 121.—Transfusion from the Central End of a Common Carotid Artery of One Dog into the Peripheral End of a Common Carotid Artery of Another, by Means of a T-Cannula.

complex methods, it could be manipulated more quickly. Their technique is as follows: "Placing bull-dog forceps on the carotids of both dogs proximally to the insertion of the cannula, and carefully removing the blood in the free ends of the arteries before inserting the cannula, prevents the blood from coming in contact with the cannula, except during the transfusion, and this contact does not start clotting. Donor and recipient, both under ether anæsthesia, are placed on the back, and the left carotid in one and the right

carotid in the other is isolated and severed. The necks of the dogs are then brought closely enough together to permit the insertion of a T-cannula in the proximal end of the carotid of the donor and in the distal end of the carotid of the recipient. The cannula is then filled with Ringer's solution, and all air-bubbles carefully removed. Everything being ready for the transfer of blood, the recipient is bled 'dry' from the proximal end of the severed carotid—that is, the carotid is left open until the flow of blood from it ceases. At this point no pulse is discernible anywhere, although a feeble cardiac impulse may still be detected. The respiration is feeble, slow, and irregular, or it may have ceased. The clamp on the carotid of the donor is now removed and the donor pumps his blood into the empty vessels of the recipient until the pulse and blood-pressure of the latter are brought up to the normal. In most of our experiments the transfusion was continued until the recipient's pressure was slightly higher than before the bleeding. The carotids of the recipient are now tied and the wound closed. The animals recover quickly from the anæsthesia, and in no case so far have any untoward symptoms, ascribable to the exchange of blood, developed.

"Obviously the recipient loses the greater part of his own blood in this procedure, and receives approximately an equal amount from the donor. Of course, we are not dealing with exact quantities. The only criterion of the quantity of blood transferred from the donor is the blood-pressure of the recipient, which, to a great extent, depends on the condition of the vasomotor centres. It is probable that the normal activity of these centres is disturbed, more or less, by the temporary anæmia of the nervous system, and the collapse of the vessels. In nearly all experiments the large dogs acting as donors were killed at the end of the transfusion."

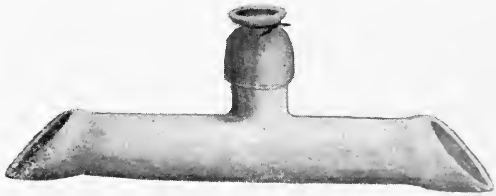


FIG. 122.—A CONVENIENT AND PRACTICAL FORM OF TRANSFUSION CANNULA.

The side-arm is for introducing salt solution to displace the air, and in use is armed with a short piece of rubber tubing, which is compressed by means of a small clamp or is closed by a rubber cap, as shown.

The operation of transfusion has been carried out in a variety of ways; trocars and cannulæ have been inserted into the vessels, and the blood led from the donor into the vessels of the recipient by

means of connecting tubes. The surfaces of all such instruments coming in contact with the blood have, as a rule, been oiled, greased, or paraffined. Sometimes connecting tubes are dispensed with, and the vessels connected by double-ended cannulæ. A very satisfactory form of such an instrument is figured (p. 265). Such transfusions can and have been made by direct anastomosis of the blood-vessels, but this is entirely unnecessary owing to the efficiency of the cannula method, and as the latter method is much simpler and quicker, it is to be recommended. It is carried out by filling the tube with salt solution and introducing one end into the central end of the ulnar artery of the donor, and the other end into the central end of the medium vein of the forearm of the recipient, and passing two 6-inch medium-sized silk ligatures about each. The artery is then permanently ligated distally with one of the ligatures, and a temporary clamp placed upon the central portion of the isolated part. The reverse technique is carried out upon the vein—that is, a temporary clamp is applied centrally before ligating peripherally, the purpose being in both cases to have the segments filled with blood to facilitate the making of the openings through which the ends of the cannula are introduced. The vessels are opened with scissors, V-shaped incisions being thus made at one cut. The apex of the incision is directed peripherally. Next, the apical flap of the artery thus produced is grasped with a pair of small dissecting forceps, and one end of the cannula, filled with 1 per cent. sodium chloride solution or 5 per cent. sugar solution, is introduced, and the ligature previously placed for this purpose is tied firmly by an assistant around the vessel over the neck of the cannula. The

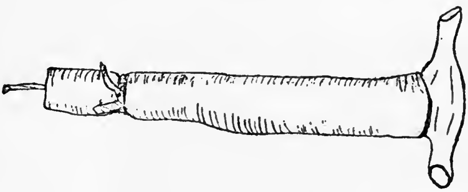


FIG. 123.—BROOKS' T-SHAPED BLOOD-PRESSURE CANNULA WITH A PIECE OF RUBBER TUBING ATTACHED TO SIDE-ARM, WHICH IS CLOSED BY A PARAFFINED COTTON PLUG WHICH HAS A STRING ATTACHED FOR A HANDLE, BY WHICH THE PLUG MAY BE WITHDRAWN.

When used, the cannula is interposed between the ends of a transected artery, restoring the circulation through the artery, and the wound is closed, leaving the side-arm protruding through the skin. After the recovery of the animal from the anæsthetic, the blood-pressure is studied by removing the ligature from around the distal end of the rubber tubing, then withdrawing the cotton plug by means of the string handle, and then quickly connecting the side-arm with the manometer and pressure-bottle.

(*Journal of the American Medical Association*, 1910, lv. 373.)

other end of the cannula is similarly inserted and tied into the vein, care being taken to see that the solution is not spilled from the tube; but in case this accident should happen, by means of an ordinary medicine dropper, previously drawn to a very fine point, the tube can be refilled before introducing it into the vein; or if the T-form of cannula shown is used, it may be filled through the stem. On removing the temporary clamps the transfusion is effected. Of course, the circulation should be watched in order to avoid overdistension of the right auricle, and the transfusion should not be too rapid. But the amount of transfusion must rest with the operator to judge from the

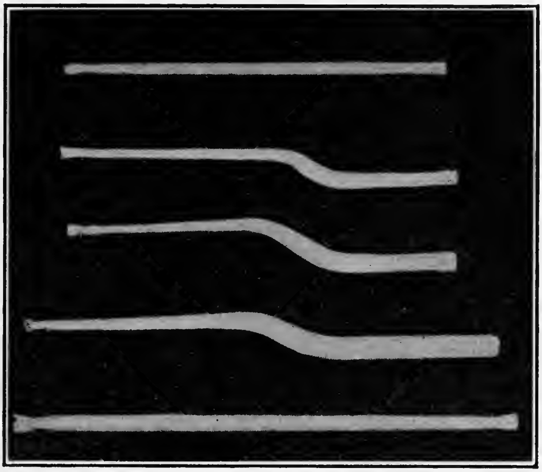


FIG. 124.—FORMS OF GLASS CANNULÆ RECOMMENDED BY BREWER AND LEGGETT FOR TRANSFUSION.

(*Surgery, Gynæcology, and Obstetrics*, 1909, ix. 293.)

indications. After the transfusion is finished the vessels are ligated and the tube removed.

Abbe (see p. 2) showed that thin glass tubes can be tolerated inside the lumen of the blood-vessels for several weeks without the occurrence of clotting.

Brooks has made use of this principle in his T-cannula method for securing wholly normal manometric blood-pressure tracings from the quiescent (unanæsthetized) animal. In this method the blood-vessel was divided and a thin-walled, short, T-shaped glass cannula, made of such a size as to fit snugly into the lumen of the artery, was inserted, restoring the continuity of the

circulatory channel, and leaving the side-arm of the T-cannula protruding from the surface of the skin. By this means the blood-pressure was measured by a mercury manometer on several successive days without the formation of an occluding thrombus in the blood-vessel or the cannula.

Boycott and Douglas have studied the fate of transfused blood in rabbits, and they conclude that as a rule such blood is destroyed when the hæmoglobin content of the recipient is high, and destruction ceases when it is low; but a number of exceptions to this have been observed. In combined bleeding and transfusion experiments the transfused blood is not destroyed, they say, unless it is superfluous.

Transfusion of blood is not without dangerous possibilities, as disease may thus be transmitted to the recipient, or the recipient's blood or other cells may be harmfully affected by agglutinins or lysins or other toxins in the blood from the donor. Careful examination of the donor and testing of the bloods together before transfusion, as pointed out by Hektoen, will minimize the danger from these sources.

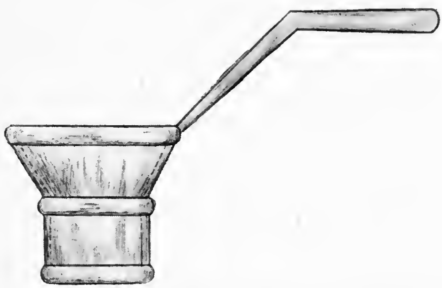


FIG. 125.—INSTRUMENT USED BY CRILE IN TEMPORARILY CONNECTING BLOOD-VESSELS BY INVAGINATION FOR TRANSFUSION. (ENLARGED.)

It has been practised with apparent beneficial results in chronic and acute anæmic conditions, as in chlorosis and after hæmorrhage. Also it has been employed in hæmophilia and in the capillary bleeding of infants.

Direct transfusion in new-born infants for capillary hæmorrhage has been practised in a number of instances by surgeons in recent years, and in general the results have been good; indeed, in several instances where much blood had been lost previous to the operation, results considered by the laity as almost miraculous have been observed. In such cases there is no doubt but that the transfused blood has served not only to aid in closing the faulty capillaries, but by augmenting the mass of blood to thus aid the circulation. But there is little doubt but that if such cases were treated in the earlier stages by intravenous injection of a relatively small quantity

of serum or defibrinated blood, equally as happy results would be obtained ; and the latter method does not involve the sacrifice of a

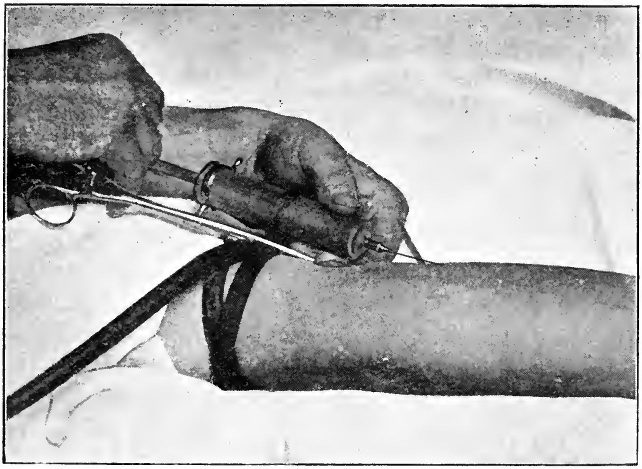


Fig. 126.—Showing Syringe Method of drawing Blood from Arm for Transfusion.

venous trunk of the babe, such as the femoral, which has been used, or of an artery, such as the ulnar or radial of the giver.

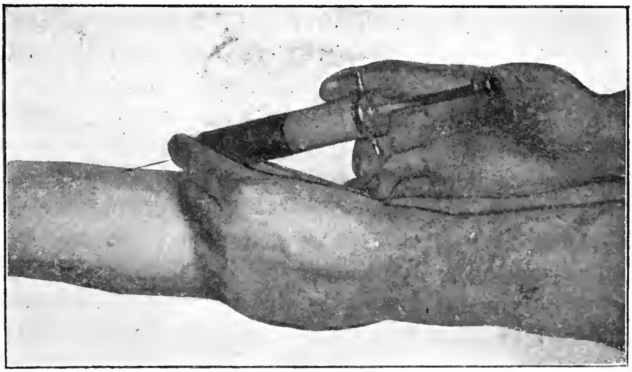


Fig. 127.—Showing Method of introducing Blood into Vein of Arm of Patient by Means of a Syringe.

From a rather extensive study of hæmophilia, Addis has concluded that the disease is due to an inherited quantitative defect in the prothrombin, whereby it is less readily activated than normal

prothrombin. Sahli believes that the lack of coagulability of blood in hæmophilia is due to a deficiency in thrombokinase, which in turn is due to a cellular anomaly both of the blood-corpuscles and the endothelial cells. At any rate, such a blood usually coagulates promptly upon the addition of fibrin ferment.

Therefore, since serum is rich in this substance, merely to render a deficient blood more coagulable, it would perhaps be equally as satisfactory to inject defibrinated blood or serum of an animal, such as a rabbit, and it is certainly a less complicated and heroic measure.

In chronic anæmic conditions the extravascular injection of blood has been followed by a very marked improvement of the condition of the patient's blood. Hüber states that one of his patients thus treated had suffered for three years with severe pernicious anæmia, and after fourteen intramuscular injections of defibrinated blood, in doses ranging from 10 to 50 c.c. extending over a period of eleven weeks, the red corpuscles showed an increase from 1,200,000 to 4,500,000 and the hæmoglobin from 18 to 92 per cent.

Proof of Survival of Engrafted Tissue from Results of Engrafted Ovaries.

The most complete evidence of survival of engrafted tissue has been obtained with ovaries in fowls. In abdominal, as well as in subcutaneous transplantations, excellent morphological results have been obtained. In iso-intra-abdominal ovarian grafts between fowls and between guinea-pigs, functional activity, in addition to anatomical structure, has been completely preserved.

Evidence of the complete functionating of such transplanted ovaries is afforded by the altered characters in the offspring. During August, 1906, the ovaries were exchanged between two black and two white leghorn pullets, weighing about 750 grammes each. One black and one white pullet were saved for controls. In January, 1907, the hens were placed in individual pens and mated with the cocks. The cocks were kept in small, tightly closed cages, except for the time they were placed in the pens to tread the hens.

Summary of Results.

No marked differences in egg-production were found between the control and operated hens nor in the fertility of the eggs.

RESULTS OF OVARIAN TRANSPLANTATION ON BODY WEIGHT AND EGG WEIGHTS IN FOWLS.*†

Fowl.	1906–1907.		1907–1908.	
	Egg Weight.	Body Weight.	Egg Weight.	Body Weight.
	Grammes.	Grammes.	Grammes.	Grammes.
B 1 (control)	60·1	1500	63·55	1350
B 2 (operated)	40·9	1250	51·17	1250
B 3 (operated)	46·6	1250	—	—
W 1 (control)	59·1	1480	59·01	1540
W 2 (operated)	49·2	1450	63·25	1750
W 3 (operated)	48·6	1250	—	—

The eggs and chicks averaged less in weight from the operated hens than from the controls. The operated hens at the beginning of the laying season were somewhat lighter in weight than the controls. In other respects no differences were observed either in the hens, eggs, or chicks. The eggs became fertile in two to four days after mating. On cessation of mating the eggs became infertile within fifteen days.

There is some evidence that hens with engrafted ovaries cease to lay before sister-hens. During the first season they may even outstrip the normal (control) hens as far as numbers are concerned, the chief constant difference being that the eggs from operated hens are lighter in weight than normal eggs from the same varieties. By the second season the eggs are nearly normal in weight, but are fewer in number—in fact, but few may be laid during the second season. In some cases egg-production ceases at this time.

Control hens (B 1 and W 1), mated to the cock of the same breed, gave uniformly black fœtuses and chicks in the case of the black, and white in the case of the white hen and cock.

The normal black chicks had greyish-yellow breasts and throats, and frequently the under-surface of the tips of the wings were light-coloured as well, but the plumage on the entire dorsal surface was *always* black. The light-coloured areas on the ventral surface were uniformly black after the first moult. Occasionally a normal black fowl may retain one or several white feathers in the tip of the wing permanently, but this is of rare occurrence, and such white feathers have not been observed in any other situation.

* All of these fowls, including the cocks, were purchased of E. G. Wyckoff, Ithaca, New York, a well-known poultry-breeder.

† *Journal of the American Medical Association*, October 17, 1908, li. 1314.

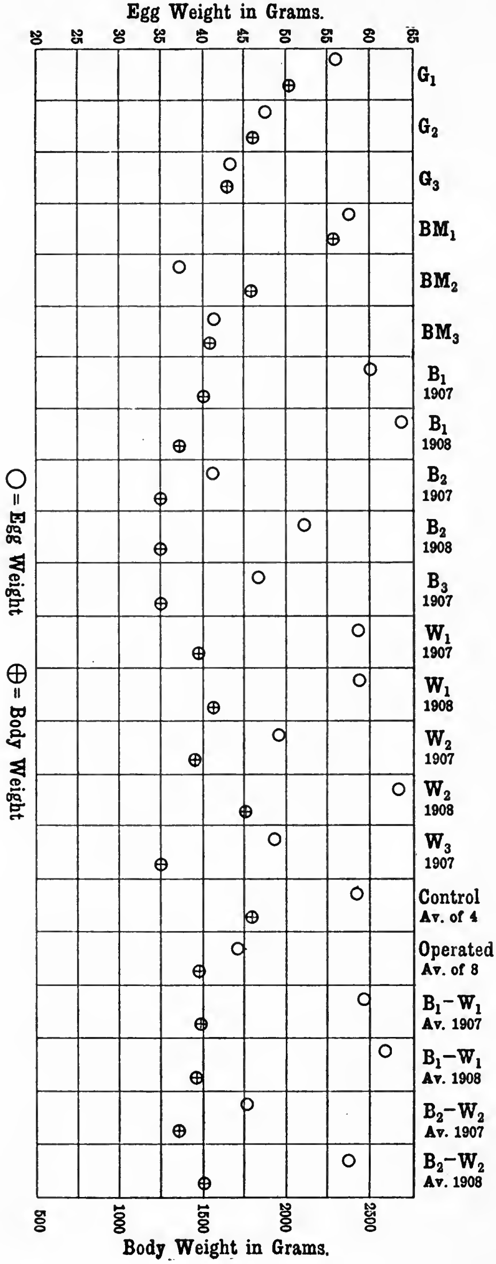


FIG. 128.—CHART SHOWING EGG AND BODY WEIGHTS.

Egg and body weight of normal hens and hens with transplanted ovaries. G_1 BM_1 and B_1 W_1 normal ; all others operated.

(*Journal of Experimental Medicine*, 1910, xii. 269.)

The normal white chicks were pure white to light buff when hatched, but after the first moult they were always pure white.

The white hen (W 2), carrying an ovary from a black hen (B 2), mated to the white cock, gave white, black, and spotted fœtuses and chicks.

The black hen (B 3), carrying an ovary from a white hen (W 3), mated to the black cock, gave ordinary black, and black fœtuses and chicks with white legs. In regard to the chicks from this hen, described as ordinary black, there was some doubt as to whether the ventral light-coloured area described for normal black chicks was not lighter and greater in extent in all cases than in the normal chicks.

The black hen (B 2), carrying an ovary from a white hen (W 2), mated to the white cock, gave about equal numbers of white and spotted fœtuses and chicks. (In all cases of very small white fœtuses, spots may have been overlooked.)

The white hen (W 3), carrying an ovary from a black hen (B 3), mated to the black cock, gave uniformly spotted chicks—*i.e.*, white chicks with black spots on the dorsal surface of the head, neck, wings, back, or on the tail.

Discussion of Results.

Colour and Markings of Chicks.

Owing to the uniform results from the controls, it is assumed that the strains of chickens used bred true to colour. Therefore, any variations in the offspring from the operated hens were due to other influences.

The fact that in all cases of the operated hens white and black or spotted fœtuses or chicks were produced (*i.e.*, the offspring showed variations from the normal in colour markings), indicates :

1. That the eggs from each of the operated hens were from the transplanted ovary. Hens B 3 and W 2 were bred to the cocks of their colour. Had some portion of their own ovary not been removed at the time of the operation (a remote possibility), and was functionating, then we would have expected solid colour offspring like the controls ; but such was not the case. In the offspring from B 3, in which the male and foster-mother were black, black predominated, but white occurred. This must have come through the white ovary. In the offspring from W 2, in which the male and foster-mother were white, white was the predominating

colour, but black occurred. The black, therefore, must have come through the black ovary, as there is no evidence that mutilation of the ovary, maternal impressions, or telegony are factors in the results. If the statement that in ordinary crossing of black and white breeds, white is dominant be accepted, then it may be assumed that the same is not true for this kind of (female) crossing, or that the original colour influence was more strongly preserved in the black than in the white ovary.

From the constancy of the results in the above two hens, we may conclude that the ovaries transplanted into the other two

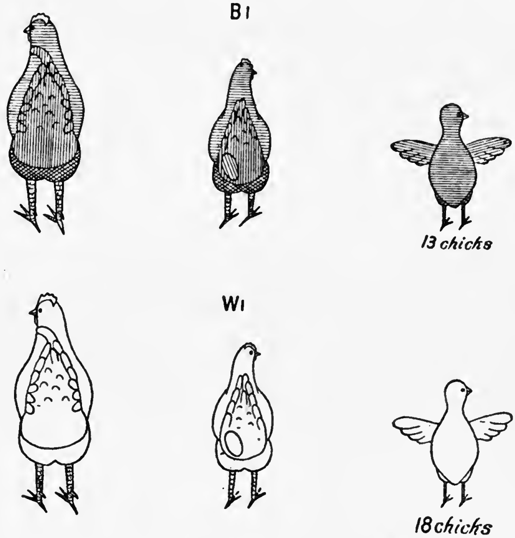


Fig. 129.—Diagram of Control Matings.
(*Journal of Experimental Zoology*, 1908, v. 563.)

hens, B 2 and W 3, were the ones functionating during the laying season.

Other results show that (1) other hens similarly operated upon, including mutilation of the ovary, showed no such variation; (2) other hens from which the ovaries were removed never laid eggs; (3) a hen from which the ovary was removed, and into which an ovary from a very widely different species was engrafted, never laid, but developed male characteristics to a very marked degree, and showed post-mortem but a small degenerated mass where the ovary was transplanted and no other ovarian tissue

whatsoever; further, all other hens from which the ovaries were removed and replaced with ovaries from a not too distantly related variety, laid eggs upon reaching maturity. Also, excepting the hen described above under (3), in which the ovary was from a very widely separated species, all hens that came to post-mortem

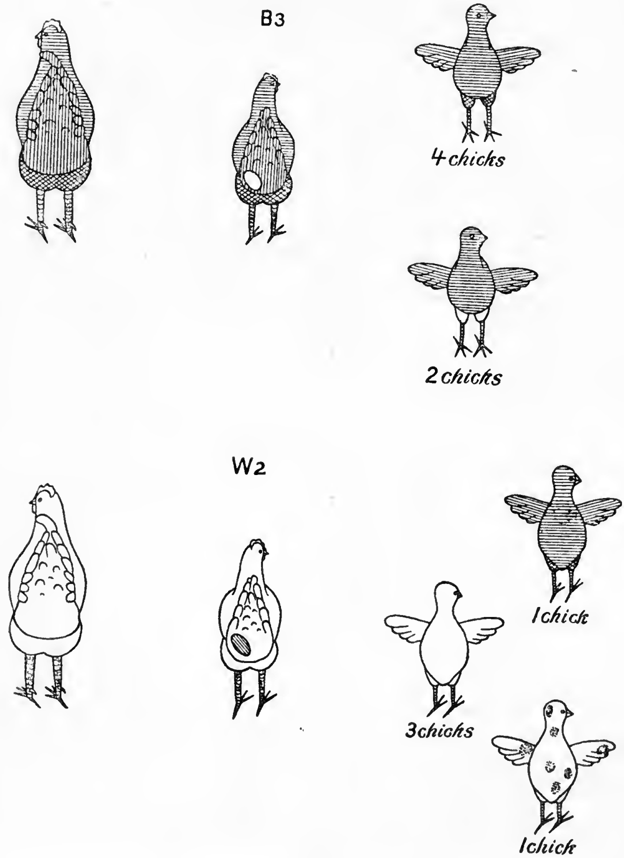


Fig. 130.—Showing that Transplanted Ovaries Function.
(*Journal of Experimental Zoology*, 1908, v. 563.)

examination in which the ovary was removed and replaced with the ovary from another hen showed abundant ovarian tissue, normal in amount and appearance, excepting that the pedicle was sometimes somewhat abnormally situated. Further, ovarian tissues were readily grown subcutaneously.

As indicated, we may conclude that the transplanted ovaries gave off ova; and that the ovaries transmitted characters of the hens from which they were removed to the resulting offspring.

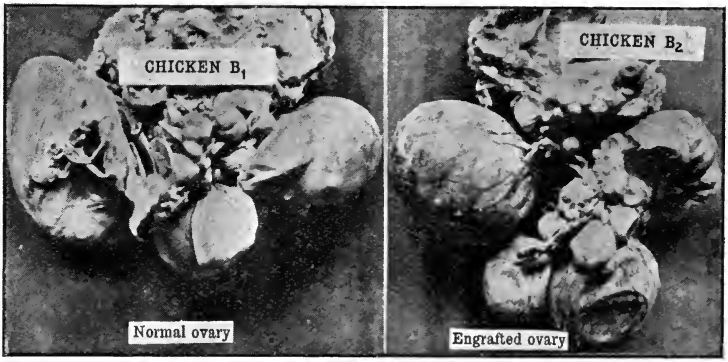


FIG. 131.—COMPARISON OF NORMAL AND ENGRAFTED OVARY FROM LAYING HENS. (*Journal of Experimental Medicine*, 1910, xii. 269.)

In at least one case, such a hen with an engrafted ovary showed a slight mass of relatively undeveloped ovarian tissue at some distance (almost a centimetre) from the large ovarian mass. From the position and attachments of the small mass, it is probable that it was a fragment of the original ovary that escaped removal at the time of the operation owing to its immaturity and location. It was far from maturity at the time of the post-mortem examination, and bore no evidence of having discharged ova. Since any such tissue that might escape removal would in all probability be in a state of relative immaturity, and since the transplanted tissue would contain relatively mature follicles, it is reasonable to suppose, conditions being equal, that such transplanted follicles would ripen earlier than the former or more immature ones. But

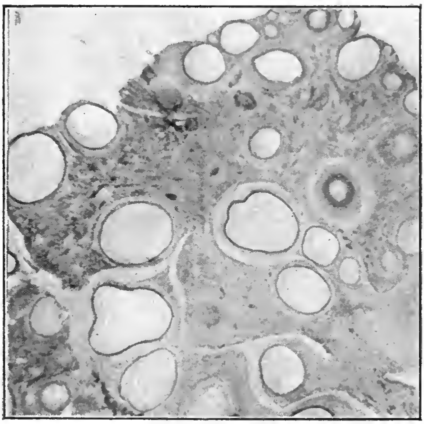


FIG. 132.—MICROPHOTOGRAPH OF OVARY OF BLACK HEN ENGRAFTED INTO WHITE HEN. Operated August, 1904; killed October, 1905.

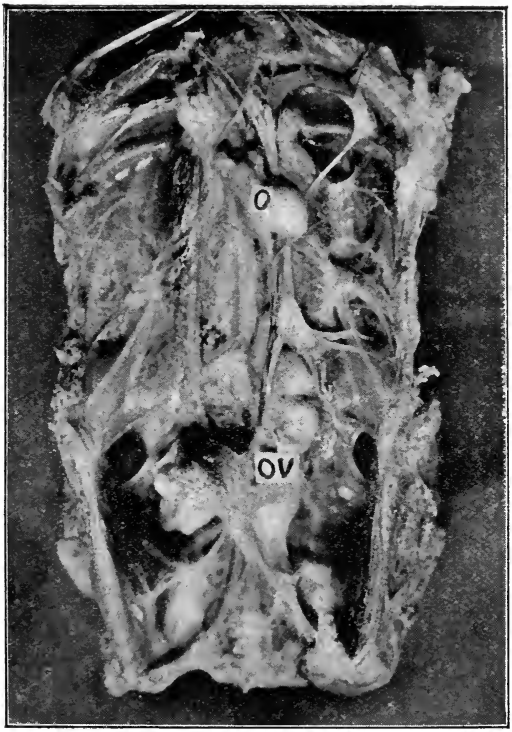


FIG. 133.—DEGENERATED ENGRAFTED OVARY.

O, Engrafted mass; OV, oviduct. Host, white Leghorn pullet; donor, buff Cochin bantam. Operated November 5, 1907; died July, 1908. (No. 35.)

FIG. 134.—MICROPHOTOGRAPH OF DEGENERATED ENGRAFTED OVARY. (No. 35.)

Note absence of normal ovarian structure.

FIG. 135.—OVARIAN TISSUE ENGRAFTED SUBCUTANEOUSLY FOR ALMOST FOUR MONTHS.

(*Journal of Experimental Medicine*, 1910, xii. 269.)

on the whole we may suppose the conditions of the transplanted tissue to be less favourable (normal) than of any that might be left *in situ*.

Yet since it is well known that interference with the nutrition of plants may accelerate the ripening of the fruit, may not the same hold for animals, and thus favour the earlier maturity of the transplanted tissue? Such questions can only be answered by experiment.

2. That the foster-mother exerted an influence on the colour of the offspring. Hens B 2 and W 3 were bred to the cock of the opposite colour—*i.e.*, of the colour of the transplanted ovary. Yet in the former the majority, and in the latter all the offspring were spotted—*i.e.*, white with black spots on the dorsal surfaces. In B 2 the male and ovary were white, and the foster-mother black; in W 3 the male and ovary were black, and the foster-mother white. In both cases white predominated in the offspring. It would seem, therefore, if we leave the question of dominance out of account, that the foster influence of the white hen was stronger than of the black hen. If, on the other hand, the foster influence is considered equal in both cases, then the results can be explained as due to the dominance of the white in the male or ovary. Professor Wilhelm Magnus, of the University of Christiania, obtained similar results on a rabbit in 1907.

Fig. 136.—Fragment of Ovary transplanted under Skin, shown in Preceding Figure, Sectioned, Magnified, and Photographed.

The character of feather-markings is of interest. In the white offspring black spots occurred on the back, neck, head, shoulders, wings, and tail in frequency in about the order given. In size they ranged from a few barbules on one feather to a patch of feathers about one centimetre in diameter. The largest spots were observed on the back and head; the smallest on the wings. The markings of the feathers were not constant even in the same individuals. Some feathers were entirely black, including the shaft, while others had

scattered markings on the vanes, involving only the barbs and barbules. In the black offspring, when white occurred, it did not appear as a spot, but some part of the body, as the leg, was solid white. No white feathers were found on the backs.*

To overthrow this evidence of functionating of the transplanted ovaries it would be necessary to show that the eggs obtained from the hens into which ovaries had been transplanted were not from such transplanted tissue, but from tissue native to the hen. Three possible explanations of the presence of such tissue might be

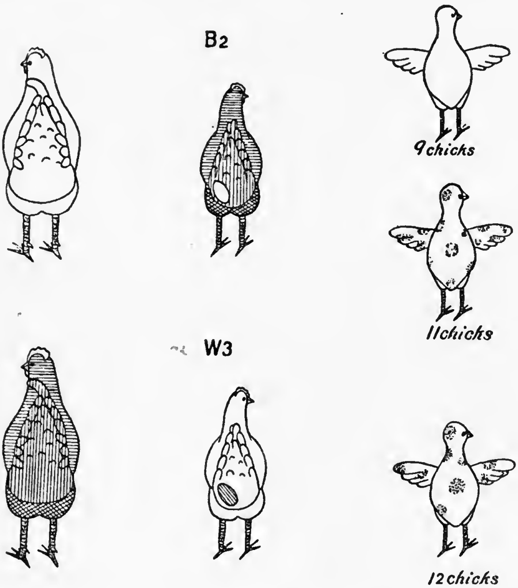


FIG. 137.—SHOWING INFLUENCE OF FOSTER-MOTHER.
(*Journal of Experimental Zoology*, 1908, v. 563.)

advanced: (1) Incomplete removal of the hen's ovarian tissue; (2) accidental intra-abdominal autografting—that is, lack of complete removal of the ovarian tissues after separation from its attachments; (3) development of new ovarian tissue, perhaps from the peritoneum.

That the first possibility may actually happen occasionally is shown (Chicken 29). A hardly visible mass of ovarian tissue was no doubt overlooked at the time of the operation, owing to its rela-

* Unless otherwise indicated, the above results have been taken from the *Journal of Experimental Zoology*, 1908, v. 563; a paper in the *Journal of Experimental Medicine*, 1910, xii. 269, is drawn upon in the following pages.

tively inaccessible position. Its relations with surrounding structures strongly indicate that it is tissue that escaped removal. A large ovarian mass, separated completely from the small mass by a glistening peritoneal surface, no doubt represents the engrafted tissue. Evidences in favour of this view are its abnormal connections and relations, and its great size and position. For in no case has a normal ovary been observed with similar connections and relationship and, owing to its large size and to its easily observed position, it cannot be seriously advanced that it is tissue that escaped removal at the time of the operation. Also, many of the follicles of this mass are many times larger than the largest follicles in the small mass, which, as already stated, probably represents tissue that escaped removal.

As illustrative of the second possibility which has been mentioned is a small isolated follicle occurring midway between the two ovarian masses described above. It has apparently simply adhered to the peritoneum, and no doubt is an autograft. The ovary was broken up more or less in removal, and this follicle was lost. Such isolated tissues have always been carefully searched for, but in none of the few instances in which they have been found have they remotely approached in size a mature follicle. Indeed, the one under discussion, though not over one millimetre in diameter, is as large as any that have been observed. This seeming lack of development may be associated with the distance from large blood-vessels, and hence deficiency in blood-supply, those observed having been adherent to the peritoneum at some distance from the dorsal blood-vessels.

As to the third possibility, the development of normally functionating ovarian tissue from soma cells, our results are emphatically against the view. For example, in no case have hens from which the ovaries have been removed laid eggs subsequently.

Again, in the single case in which degeneration of an ovary engrafted into a fowl has been observed no eggs were laid. (The host was a white Leghorn pullet ; the donor a buff Cochin bantam.) A minute post-mortem examination of the fowl (Chicken 35), in which degeneration of the engrafted ovary occurred, did not reveal any vestige of normal ovarian tissue nor abnormality of any kind save the degenerated engrafted mass. Furthermore, all control hens have produced eggs.

We may also take into account the evidence furnished by castration or spaying of various animals. As is well known, removal of

the ovaries from a young female is followed by a subnormal development of female characters, including sterility. The general effect on development may be so strong that on reaching adult age the unsexed animal may present qualities as strongly masculine as feminine. No such result was observed in hens into which ovaries had been engrafted after removal of their own ovaries, except in the case of degeneration of the tissue (Chicken 35 ; see p. 277). The results in this case were exceedingly pronounced. The pullet rapidly acquired not only the outward anatomical features of a cock—cock's-comb, wattles, long hackle and tail feathers, rapidly developing spurs, carriage, etc.—but the behaviour as well was that of a male. It exhibited a pugnacious attitude toward other cocks, was attracted by hens, and even went so far as to tread hens as a cock. (It may be remarked that it would seem to be difficult to harmonize these phenomena with the more or less definitely enunciated theory which attributes male characteristics to the internal secretion of the interstitial cells of the testicles.)

Another hen (W 2) is especially interesting in this respect. During the first season (1906-07) she laid many fertile eggs ; during the second season (1907-08) she laid but a single egg. Since this time she has ceased to lay. She has developed an appearance intermediate between a hen and a cock, being on the whole more feminine than masculine. In behaviour she has developed no pronounced male characteristics, such as were observed in the case of Chicken 35. In view of these facts, ultimate anatomical findings in her case will be of interest. Her appearance and behaviour denote a loss of feminine rather than an acquisition of positive masculine qualities—that is, she presents certain characters which, in the absence of positive feminine qualities, we regard as more or less masculine, though positive masculine qualities do not seem to be present.

In a way we may—provisionally, at least—regard the condition as due to an unmasking of characters, judgment being normally biased by the positive feminine qualities.*

On the whole, therefore, we may be reasonably certain that ovarian tissue engrafted into fowls, as in these experiments, may develop and preserve its functional powers to a high degree.

Furthermore, offspring derived from such engrafted ovarian tissue are of great interest, not only in the direction indicated in the preceding pages, but from the standpoint of the nature of, and the

* *Cf.* Darwin, "Animals and Plants under Domestication," 1899, ii. 27.

mechanisms concerned in transmission of, hereditary characters. And since such offspring are unique in being somewhat of a character of graft hybrids in plants, a discussion of the subject will be presented for the reader who may be interested in this phase of the work.*

The importance of accurate information on the subject of graft hybrids has long been recognized. It was clearly appreciated by Darwin, who wrote as follows: "I will therefore give all the facts which I have been able to collect on the formation of hybrids between distinct species or varieties without the intervention of the sexual organs. For if, as I am now convinced, this is possible, it is a most important fact which will sooner or later change the views held by physiologists with respect to sexual reproduction." †

After citing numerous instances of the production of graft hybrids in various plants, Darwin concludes with a rather extensive review of the results in potatoes (pp. 410-412). His summary and deductions are so clear and logical that they are quoted in full:

"Anyone who will attentively consider the abstract now given of the experiments made by many observers in several countries will, I think, be convinced that by grafting two varieties of the potato together in various ways hybridized plants can be produced. It should be observed that several of the experimenters are scientific horticulturists, and some of them potato-growers on a large scale, who, though beforehand sceptical, have been fully convinced of the possibility, even of the ease of producing graft hybrids. The only way of escaping from this conclusion is to attribute all the many cases to simple bud variation. Undoubtedly the potato . . . does sometimes, though not often, vary by buds; but it should be especially noted that it is experienced potato-growers, whose business it is to look out for new varieties, who have expressed unbounded astonishment at the number of new forms produced by graft hybridization. It may be urged that it is merely the operation of grafting, and not the union of two kinds, which causes so extraordinary amount of bud variation; but this objection is at once answered by the fact that potatoes are habitually propagated by the tubers being cut into pieces, and the sole difference in the case of graft hybrids is that either a half or a smaller segment or a cylinder is placed in close apposition with the tissue

* A paper "On Graft Hybrids," *Annual Report of the American Breeders' Association*, 1911, vi. 356.

† *Loc. cit.*, i. 417.

of another variety. Moreover, in two cases the young stems were grafted together, and the plants thus united yielded the same results as when the tubers were united. It is an argument of the greatest weight that, when varieties are produced by simple bud variation, they frequently present quite new characters; whereas, in all the numerous cases above given, as Herr Magnus likewise insists, the graft hybrids are intermediate in character between the two forms employed. That such a result should follow if the one kind did not affect the other is incredible.

"Characters of all kinds are affected by graft hybridization, in whatever way the grafting may have been effected. The plants thus raised yield tubers which partake of the widely different colours, form, state of surface, position, and shape of the eye of the parents; and according to two careful observers they are also intermediate in certain constitutional peculiarities. But we should bear in mind that in all the varieties of the potato the tubers differ much more than any other part.

"The potato affords the best evidence of the possibility of the formation of graft hybrids, but we must not overlook the account given of the origin of the famous *Cytisus adami* by M. Adam, who had no conceivable motive for deception, and the exactly parallel account of the origin of the Bizzarria orange—namely, by graft hybridization. Nor must the cases be undervalued in which different varieties or species of vines, hyacinths, and roses, have been grafted together and have yielded intermediate forms. It is evident that graft hybrids can be made much more easily with some plants, as the potato, than with others—for instance, our common fruit-trees; for the latter have been grafted by the million during many centuries, and though the graft is often slightly affected, it is very doubtful whether this may not be accounted for merely by a more or less free supply of nutriment. Nevertheless, the cases above given seem to me to prove that under certain unknown conditions graft hybridization can be effected.

"Herr Magnus asserts with much truth that graft hybrids resemble in all respects seminal hybrids, including their great diversity of character. There is, however, a partial exception, inasmuch as the characters of the two parent forms are not often homogeneously blended together in graft hybrids. They much more commonly appear in a segregated condition—that is, in segments either at first or subsequently through reversion. It would seem that the reproductive elements are not so completely blended by grafting

as by sexual generation. But segregation of this kind occurs by no means rarely, as will be immediately shown in seminal hybrids."

Thus, it would seem that graft hybrids in plants are by no means rare, and in some species—*e.g.*, the potato—not difficult of realization. But it is worthy of note that experiments on graft hybridization are not always successful. For example, Romanes says: "I made thousands of experiments in graft hybridization (comprising vines, bulbs of various kinds, buds, and tubers), but with uniformly negative results." Such negative results, however, cannot be considered as disproving the numerous positive results previously obtained under rigid experimental conditions.

We may now consider the evidence obtained from animals. Romanes endeavoured to obtain hybrids in animals by transplanting ovaries, but was unsuccessful.*

Romanes' views and experiments along these lines are interesting. They are briefly, in his own words, as follows: "When first led to doubt the Larmarckian factors, now more than twenty years ago, I undertook a research upon the whole question. As this research yielded negative results in all its divisions, I have not hitherto published a word upon the subject. With animals I tried a number of experiments in grafting characteristic congenital tissues from one variety on another, and in rabbits and bitches the transplantation of ovaries of newly-born individuals belonging to different well-marked breeds. This latter experiment seems to be one which, if successfully performed (so that the transplanted ovaries would form their attachment in a young bitch puppy, and subsequently yield progeny to a dog of the same breed as herself), would furnish a crucial test as to the inheritance or non-inheritance of acquired characters. Therefore I devoted to it a large share of my attention, and tried the experiment in several different ways. But I was never able to get the foreign ovary, or even any part thereof, to graft."

Even had Romanes been successful in obtaining offspring from a female bearing ovaries from an individual of another breed, the manner of breeding that he had in mind—viz., mating with a male of the same breed as the "foster-mother"—would have warranted the conclusion that the transplanted ovary functioned, but not that there was a "foster" or "soma" influence.

Though interesting, his views as to the value of the demonstra-

* "Darwin and After Darwin," 1895, ii. 143.

tion of such "foster" influence, in substantiation of the Lamarckian principles—*e.g.*, "the whole issue as between the rival theories of heredity will be settled by the result of a single experiment"—are not warranted. It would seem more rational to suspect as factors in the production of the phenomenon influences which here may be indicated by the general term *nutritional* rather than what may be termed *specific inherent.*

Many others have made similar attempts to engraft ovaries, but with the exceptions noted below they were for the most part unsuccessful.

Heape seems to have been the first to get definite results in this field. From an Angora doe rabbit fertilized thirty-two hours previously by an Angora buck two segmenting ova were removed and immediately transferred to the Fallopian tube of a Belgian hare covered three hours previously by a Belgian buck. At full term the Belgian doe gave birth to six young, four resembling herself and mate, the other two being undoubted Angoras. Heape observed no likeness between the two kinds of young.

In a subsequent experiment segmenting ova from a Dutch doe covered twenty-four hours previously by a Dutch buck were transferred to the Fallopian tube of a Belgian doe previously covered by a Belgian buck. Seven young resulted—five Belgians and two irregularly marked Dutch. On breeding a "thoroughbred" Dutch doe to the Dutch buck used in this experiment a litter was produced that were as badly marked as the Dutch foster-children.

In short, Heape concluded that the uterine foster-mother exerts no modifying influence upon her foster-children, in so far as can be tested by the examination of a single generation. These experiments, though brilliant in their conception, are open to so many errors that any conclusions from them are unwarranted. For example:

1. It would be impossible to be certain in any particular instance that the transplanted ova were completely fertilized before their removal from the Fallopian tubes or uterus.

2. If incompletely fertilized eggs were transplanted, the process might be completed by sperm previously discharged into the foster-mother.

3. Sperm might be transferred with the egg to the "foster-mother," thus raising the possibility of cross-fertilization in the latter.

The first and second of these possible sources of error might have

been eliminated by transplanting the supposedly fertilized eggs into virgin females in heat.

The above criticisms are clearer when it is recalled that in plants pollen may affect tissue of the parent. But of more significance is the fact that a single grain of pollen may not fertilize to the extent of giving germinable seed. Gärtner found that on a Malva 30 grains did not fertilize a single seed, but when 40 grains were applied to the stigma a few seeds of small size were formed. He believed that many grains of pollen are first expended in the satiation of the pistil and ovarium.

Similar observations have been made on animals. For example, Quatrefages has shown in the case of a mollusc (*Teredo*, or shipworm), and Newport for Batrachians that more than one sperm cell is necessary to fertilize an egg. When too few are applied to the eggs of Batrachians, the embryos are never fully developed. Also; the rate of segmentation of the egg is influenced by the number of the sperm cells. It should be remembered that purely physical and chemical agents may cause changes in eggs that may resemble early developmental processes observed in incomplete fertilization by sperm (artificial parthenogenesis).

In the case of the higher animals, the evidence is less complete; but sufficient is known to properly lead to the conclusion that more than one sperm cell may be necessary for the complete fertilization. For example, Harper has shown that polyspermy normally occurs in the pigeon, and that twelve or more sperm cells affect the egg. Patterson has obtained similar results for hens (chickens), and he concludes that "polyspermy, accompanied by accessory cleavage, normally occurs in hen's egg."

Satisfactory evidence in the case of mammals is yet lacking. Wilson states that more than one sperm cell may enter the egg, but he does not believe this is a normal occurrence.

For some years I conducted experiments on pure-bred swine to discover if results thus obtained would throw any light on this interesting question. I am only able to state that the results thus far obtained indicate the occurrence of what may provisionally be termed "polyspermy, or polypaternity." * Although microscopical investigation is of interest and value, it is only by breeding experiments that the true significance of the phenomenon can be determined.

* Recently Professor Kellog has reported similar results from double mating of silkworm moths (*Science*, 1911, N.S., xxxiii. 783).

Again, the possible influence of the accessory sexual secretions is to be taken into account. The literature on this subject is meagre, and but little of a conclusive nature, so far as I am aware, has been made out. In the case of the male, it is claimed by Walker that "the ova of rabbits, guinea-pigs, and dogs, can be successfully fertilized by injecting into the vagina a mixture of sperm from the epididymis and physiological salt solution." Steinach claims that the prostatic secretion greatly favours motility in the spermatozoa. It has been suggested that the secretion may tend also to render alkaline the medium in which the germ cells must swim, favouring in this way the sperm cell, as it is known that an acid reaction is injurious. The favouring influence of the alkaline reaction is shown by Loeb's experiment of adding star-fish sperm to Strongylocentrotus eggs in artificial sea-water to which sodium hydroxide had been added. The eggs underwent changes indicating imperfect fertilization.

Morgan discusses the factors involved in the entrance of the spermatozoon in the lower forms. His position that "much still remains obscure" is well taken.

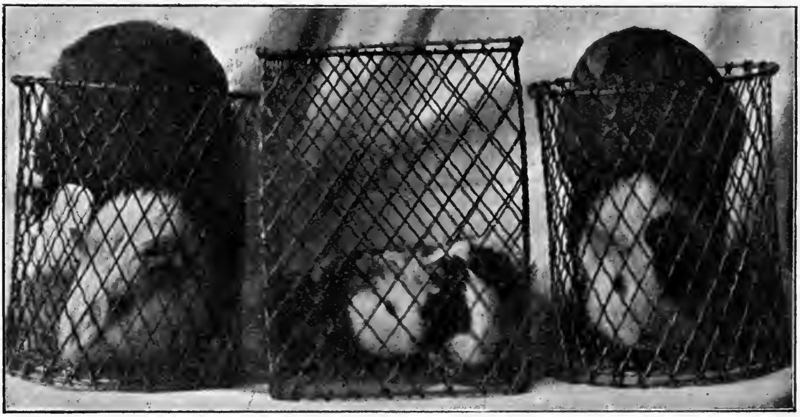
It has been suggested that fertilization may be due to a catalytic or enzyme action. Gies added sperm extracts to eggs, with negative results. He remarks, however, that "these negative results cannot be put forward as proof that there are no enzymes in spermatozoa which function during the normal process of fertilization." O. H. Brown performed some experiments to test the view that the process of fertilization might be due to the "acceleration of the enzyme action of the eggs by virtue of the presence of the enzymes of the spermatozoa." These results were, in the words of the investigator, "in no measure conclusive." Lyon has reported results indicating the presence of a kinase or activating body in sperm which increases the catalytic action of eggs on hydrogen peroxide. It is, therefore, plain that we cannot deny the possibility of unorganized substances in the sperm playing an *active* rôle in the process of fertilization.*

In commenting on Heape's results, Romanes remarks that, since rabbits crossed in the ordinary way never throw intermediate characters, the results are without significance as regards the inheritance of acquired characters. Notwithstanding Heape's later results, in which he disproved Romanes' main premise, Vernon

* See paper by writer in Proceedings International Association of Instructors and Investigators in Poultry Husbandry, 1911.

concludes that Heape's results are probably of not very great value "so far as they relate to the production of somatic variations by change of environmental conditions during embryonic development."

In 1906 Dr. Robert Morris reported the birth of a child in a woman from whom the ovaries had been removed and replaced with ovarian tissue from another. Inspired by this result, Wilhelm Magnus, of Christiania, removed and transplanted the ovaries in twenty-five rabbits. Out of this number, one bore young. The first litter gave evidence of foster-mother influence. The animal was bred a second time, but died before the young



FATHER. OFFSPRING. MOTHER. OWN OVARIES REMOVED AND REPLACED BY SISTER'S.

FIG. 138.—OFFSPRING FROM ENGRAFTED OVARY.

were born. The latter, however, were sufficiently developed to show the colour-markings, and they, too, gave evidence of the foster-mother influence. At post-mortem examination one of the transplanted ovaries was found to have degenerated, but the other was in fair condition.

My own results are, so far as I am aware, the most complete thus far reported, but since they are given in considerable detail in the preceding pages, it will suffice to repeat here that apparently the transplanted ovaries functionated, and the foster-mother influenced the markings of the chicks.

I have exchanged the ovaries between fowls, dogs, cats, rabbits, guinea-pigs, rats, mice, and frogs, but in no case other than in fowls and in guinea-pigs have offspring resulted. Good histological structure has been preserved in some cases.

In conclusion, Darwin's explanation of the characters presented by plant graft hybrids (as set forth by him, and quoted in the first part of this paper) is of interest, and in his own words is as follows :

FIG. 139.—TESTICULAR TISSUE ENGRAFTED SUBCUTANEOUSLY FOR ALMOST FOUR MONTHS.

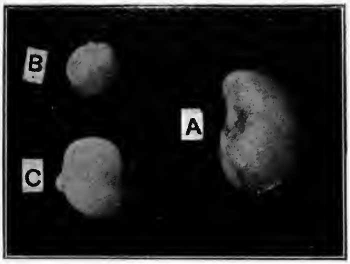


FIG. 140.—ENGRAFTED TESTICULAR TISSUE.

A, Left testicle removed and reimplanted at original site ; B, fragment of right testicle left *in situ* ; C, portion of right testicle removed and implanted under skin of left shoulder. Operation December 15, 1908 ; specimens taken, April 5, 1909.

(*Journal of Experimental Medicine*, 1910, xii. 269.)

" Finally, it must, I think, be admitted that we learn from the foregoing cases a highly important physiological fact—namely, that

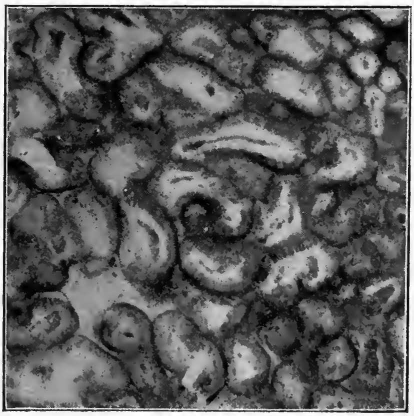


FIG. 141.—FRAGMENT OF TESTICLE SHOWN IN PRECEDING FIGURE. SECTIONED AND MAGNIFIED.

the elements that go to the production of a new being are not necessarily formed by the male and female organs. They are

present in the cellular tissues in such a state that they can unite without the aid of the sexual organs, and thus give rise to a new bud partaking of the characters of the two parent forms."

One should not consider animal offspring from engrafted ovaries as identical with the graft hybrids of plants described by Darwin. The writer has used the term provisionally, and as a matter of convenience. If, for example, it is shown that non-fertilized or completely fertilized eggs (or embryos) can be transferred into another animal and survive, and if such resulting offspring show "foster" influence, then a certain parallelism will be established between

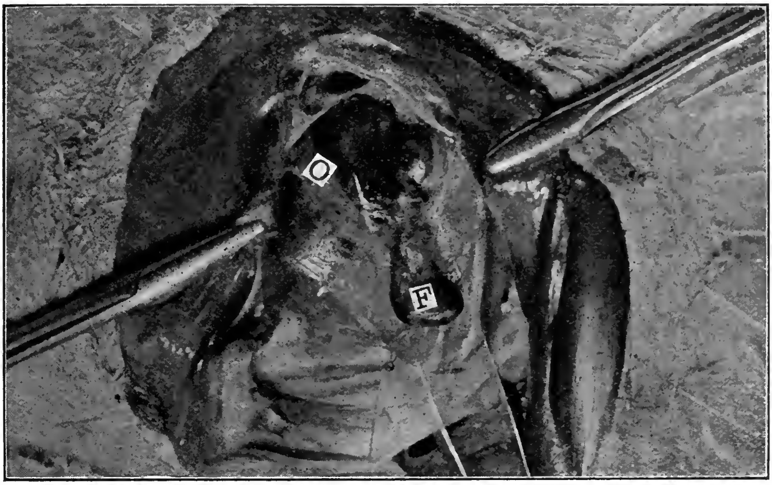


Fig. 142.—Common White Hen into which a Seven-Day-Old Plymouth Rock Fœtus was engrafted, May 4, 1909. Photographed May 21, 1909.

The Fœtus (F) showed no signs of life when examined seventeen days after the operation. Apparently retrogressive processes were present, and it was gradually being absorbed. O, Graaffian follicle.

animal and plant "graft hybrids." With positive results achieved in this direction, repetition of the experiments with animals bearing engrafted ovaries would surely follow. Finally, with the completion of suitable experiments with re-engrafted ovaries, data adequate to definitely advance our knowledge in this direction might be acquired. There seems to be a possibility that some information along these lines may be obtained by transplanting testicular tissue.

The whole foundation of heredity, both as to exactly what comprises heredity and what constitutes its transmission, is obviously raised in this discussion. From a physiological standpoint the question of nutrition seems to be of prime importance.

Survival of Animal Tissues In Vitro.

The survival of animal tissues *in vitro* is a subject that until recently has received but relatively little attention, though accounts of such experiments have been published.

It is known that bits of plant tissues may be propagated by engrafting into the same or different plants from which they were removed or by placing them directly in contact with water or moist

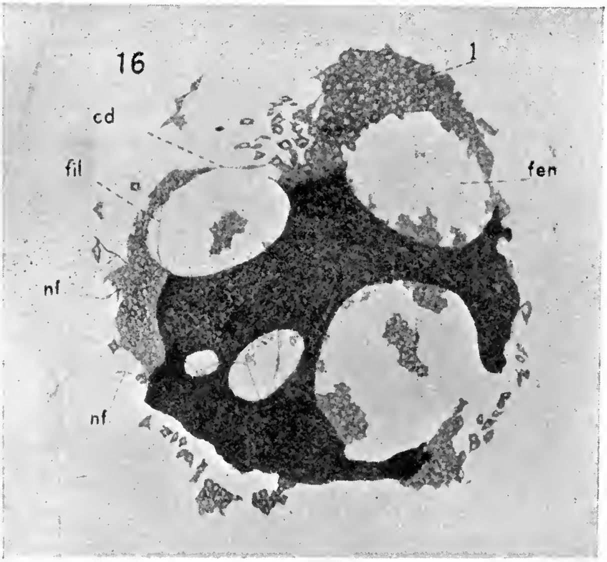


FIG. 143.—WHOLE PIECE OF TISSUE (MEDULLARY CORD, WITH SMALL PORTION OF MUSCLE PLATES ATTACHED) IN ISOLATED LYMPH, TWO DAYS AFTER PREPARATION.

The dark area represents a thick opaque mass of tissue. Thin sheets of cells (1) and isolated cells are shown on all sides. *nf*, Nerve fibres projecting out into lymph from under the masses of cells; *fil*, threads of hyaline protoplasm bridging spaces between masses of cells; *cd*, band of cells in single file. Tissue from pipiens embryo in lymph (Harrison).

(*Journal of Experimental Zoology*, Vol. ix., No. 4, p. 787.)

earth. Thus it is possible to bring about the formation of a complete individual from a fragment of plant tissue. And the same is true of certain low forms of animals. For example, earth-worm tissue may be successfully engrafted, so that it is possible to cause an individual to present two heads or two tails (Morgan). And, further, non-engrafted fragments of tissue of such animals may survive and even grow. Born successfully engrafted tadpoles together in various ways. Harrison united parts of tadpoles of

different varieties so successfully that the composite tadpole underwent transformation into a frog.

Harrison devised a method which enabled him to preserve the vitality of frog tissues to such an extent that such tissues were capable of actual growth after complete isolation. He placed the isolated tissues in drops of lymph, using hollow-ground slides for mounting. The lymph soon clotted, and with the microscope he observed the growth of nerve axis-cylinder processes, wandering and proliferation of connective tissues and epithelial cells, and the differentiation of striated muscle cells.

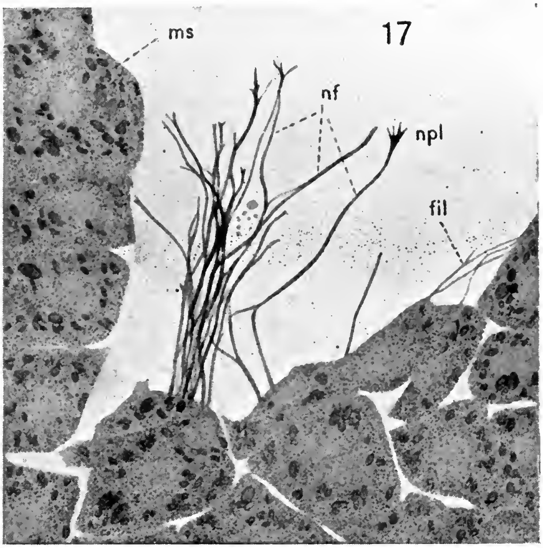


FIG 141.—PLEXUS OF NERVE FIBRES GROWING OUT FROM A MASS OF TRANSPLANTED MEDULLARY CORD. TWO DAYS AFTER OPERATION. Pipiens Tissue, Lymph Underminded (Harrison, × 350). (*Journal of Experimental Zoology*, Vol. ix., No. 4, p. 787.)

Sufficient quantities of lymph being difficult to secure, under Harrison's direction and in his laboratory Burrows succeeded in substituting blood-plasma for lymph as a cultivation medium, and further to confirm Harrison's results on frog tissues and to grow chick tissues. Later, Burrows with Carrel repeated the experiments with mammalian tissues, and reported similar results. Of their results they write as follows : " Many cultures from glandular organs were made and grew rapidly. The cultivation of the thyroid of adult dogs was very easy. After thirty-six or forty-eight hours long

fusiform cells protruded at one or several points from the edges of the tissues. Often new polygonal cells also could be seen on the upper surface or on the edges of the thyroid. After the fifth and sixth days the cultures were generally in full and sometimes wild vegetation, which lasted as long as the plasmatic medium was in good condition." In giving results with renal tissue they write: "Two plasmatic media were inoculated with small fragments of a kidney of a young cat. Twelve hours later fusiform cells were protruding from the tissue. After twenty-four hours a great many cells had invaded the plasma all about the renal substance. One day later the cultures vegetated wildly. On the fifth day one of the cultures was fixed and stained with hematoxylin. We saw many karyokinetic figures in the cells which had proliferated through the plasma. A tube had begun to grow from the tissue into the medium. The cells showed a condition of great activity. The other culture was allowed to live to the sixth day, and an exceedingly active growth of the cells took place. In the morning we observed a few tubes growing from the renal substance into the plasma; in the evening they were very much longer, and curved at their blind ends. . . . They had the appearance of renal tubules."

Lambert and Hanes have grown mammalian tissues in alien serum—*e.g.*, rat spleen in dog plasma. Lewis and Lewis have successfully grown tissues of warm-blooded animals not only in plasma, but on nutrient agar and in various solutions, including plain sodium chloride solution.

Essentially, Harrison's method of cultivation of animal tissues *in vitro* consists in placing bits of tissue in unclotted lymph or plasma in a receptacle permitting observation without disturbing the preparation, as a hollow ground-slide, and taking precautions to prevent evaporation and to maintain a suitable temperature. Of course, bacterial or other contamination is avoided as much as possible.

Harrison drew some very interesting and important conclusions from his studies, especially upon the growth of nerves. Though it is not possible to say at the present time whether such studies upon tissues of higher animals will prove as fruitful, they are very alluring.

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CHAPTER IX

RESUSCITATION

A CONSIDERATION of the subject of resuscitation is an essential division of blood-vessel surgery, for the surgeon may be called upon at any time not only to prevent death from failure of the circulation, but he may also be called upon to restore a circulation that has failed. In other words, a surgeon may be called upon to restore a patient from a state of clinical death to life, as after clinical death from a general anæsthetic, as chloroform, or from drowning; and success in this field requires not only an accurate knowledge and understanding of certain facts and principles of the physiology of the circulation, but ability to observe and rapidly interpret clinical circulatory phenomena, and to act quickly. Therefore, the subject of treatment of the circulation in conditions in which failure is prone to occur and methods of resuscitation will be outlined, and a brief account of the major practical considerations of the physiology of the circulation as viewed from this standpoint will be given.*

Some Practical Considerations of the Physiology of the Circulation.

Morphologically, the circulatory apparatus consists of a central pump, the heart, connected with a system of elastic tubes, the bloodvessels, divided into two sets—the arteries, which conduct the blood from, and the veins which return it to, the heart. These two systems of tubes communicate through the capillaries. The work of the heart is largely expended in overcoming the resistance offered to the flow of the blood through the arteries and capillaries. The return of the blood through the veins is in part dependent

* A paper presented before the St. Louis Medical Society, and published in the *Interstate Medical Journal*, 1908, xv., No. 6, is freely drawn upon in the following pages.

upon other factors—*e.g.*, aspiration of the thorax and general muscular contraction.

The pressure in the arterial system, under normal conditions, is largely dependent upon two factors—the work of the heart and the peripheral resistance. A third factor of interest in this connection is the mass of blood.

The work of the heart—*i.e.*, the rate and force—is normally under nervous control. The nerve impulses originate in the upper part of the spinal cord, the medulla oblongata. In the normal animal, if the arterial blood-pressure be mechanically increased, as may be done by compressing the aorta, the working of the heart is automatically decreased ; while if the pressure be lowered, as by releasing the aorta, the working of the heart is increased. In both instances the mean arterial pressure tends to remain constant. This control is normally exercised by the extrinsic cardiac nervous mechanism, in virtue of impulses originating in the central nervous system. It is an interesting fact that after the extrinsic cardiac nerves are cut—viz., the vagi and accelerantes—and even in the heart removed completely from the body, there is evidence that such regulation of the rate and force of the beat to changes in arterial pressure is still preserved. Hence it appears that within the heart a mechanism exists which, in the absence of any connection with the central nervous system, is capable of governing the working of the organ.

As to the mechanism of control of the peripheral resistance, it is well known that alteration in this occurs under normal conditions chiefly through tonic changes in diameter of the arterioles. This is effected by nervous impulses that originate in the medulla oblongata, and pass along nerve-fibres to the muscular cells situated in the walls of the arterioles. The following experiment will serve to emphasize the chief practical considerations :

Efficiency of Perfusion of the Coronary Arteries in Starting the Isolated Mammalian Heart.—This may be demonstrated by removing the heart from the body, and suspending it from a cannula tied in the root of the aorta. It soon ceases to beat. The animal's blood, having been collected, is defibrinated, and either alone or mixed with several volumes of 0·9 per cent. sodium chloride solution at a temperature of about 35° C. is injected through the cannula into the root of the aorta under a pressure equivalent to a column of mercury about 160 millimetres in height. Thus, perfusion of the coronary vessels is effected, and the heart soon begins to beat strongly.

The essential condition primarily involved in causing a quiescent heart to contract by coronary perfusion appears to be a stimulating action associated with the pressure of the fluid in the capillaries of the heart. This is evidenced by the fact that perfusion with inert fluids, such as hydrogen gas or paraffin-oil, is capable of causing a quiescent heart to beat, providing, of course, that it has not been in that condition too long a time. But since such an inert fluid is unable to maintain nutrition, the heart soon again becomes quiescent.

Isotonic salt solutions have been extensively used for perfusing the heart. Chief among these may be mentioned those containing sodium, calcium, and potassium salts in the amounts in which they

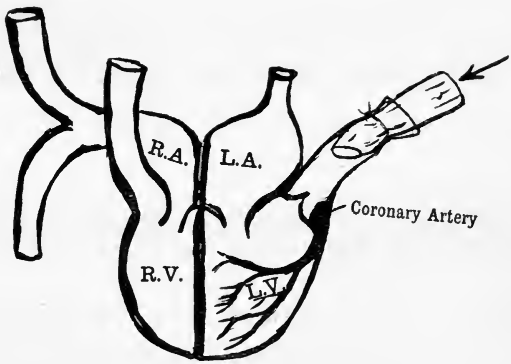


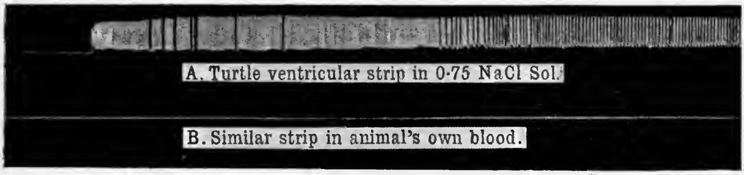
Fig. 145.—Showing Cannula inserted into Aorta for Perfusing the Coronary Arteries in an Isolated Mammalian Heart.

occur in the blood, as determined from the analysis of blood ash. These may be taken as representatives of the class of truly inorganic solutions.

The chief difference in the result with such salt solutions, compared with the results obtained by perfusion with inert fluids (gas, oil, mercury), is of a quantitative character. The heart may beat more strongly and for a longer time with salt solution, but this may be largely explained by reason of its greater carrying capacity for the waste metabolic products of the heart tissues, by its carrying a certain amount of oxygen in solution to the heart, and by the fact that the solution may have a stimulating action on the cells of the heart by reason of a direct chemical action of the salts. Or some physical difference, as degree of molecular concentration, may contribute to the result.

It is interesting to note the difference in behaviour of quiescent heart tissue placed in defibrinated blood and of such tissue placed in any of the inorganic salt solutions.

To show the stimulating action of so-called isotonic sodium chloride solution on the heart, similar strips of muscle from the ventricle of a turtle's heart are prepared and attached to levers arranged to mark on a smoked paper. Both strips are quiescent. On submerging one of the strips in 0·75 per cent. sodium chloride solution, and the other in the animal's own blood, which has been collected



A, Record of behaviour of strip of heart muscle of turtle in 0·75 NaCl solution. B, same in animal's own blood.

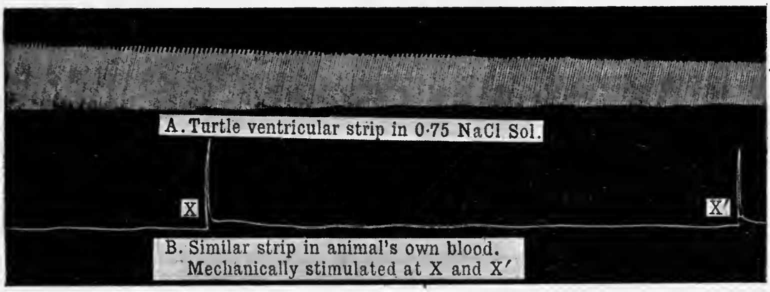


FIG. 146.—SHOWING BEHAVIOUR OF HEART MUSCLE IN BLOOD AND IN SALT SOLUTION.

and defibrinated for that purpose, it is observed that the first-mentioned strip soon begins to contract, while the other strip remains quiescent. On mechanical stimulation the strip in blood contracts. Also, if the blood be removed and replaced with salt solution, the strip begins to contract rhythmically. This is very strong evidence that such salt solutions are not inert, but stimulating. They cannot be considered as nutritional, excepting for the small volume of oxygen they carry. Therefore their action is to quickly exhaust the heart. But the action does not stop there. The cells are caused to lose their vitality rapidly (see Chapter V.).

The results of Cristiani on the preservation of thin slices of tissue for grafting strongly corroborate this view. But these experiments are discussed elsewhere (p. 120). And it is further supported by the writer's results of perfusing the kidneys with salt solution, and by the observations of Policard, who studied the histological changes produced in bits of renal tissue under the influence of such solutions (p. 121).

Another class of artificial perfusion fluids is prepared by the addition to inorganic salt solutions of substances calculated to render their physical characters more nearly the same as blood—*e.g.*, the addition of gum arabic or boiled starch.

Still a third class is prepared with the view of supplying food material to the tissues—*e.g.*, Locke's solution, which differs essentially from the inorganic salt solutions in that it contains a small amount of dextrose, which theoretically will be oxidized. This has been independently demonstrated by Dr. McGuigan in our laboratory to be true for skeletal muscle, and by Dr. Locke of England for cardiac muscle (p. 122).

Another similar solution is prepared by the addition of serum proteid to the inorganic salt solutions, so that the composition is more nearly like blood-serum. It is generally agreed that any of the above solutions should be rendered slightly alkaline for the best results. Another class of solutions, partaking of the characters of all those just described, consists of solutions made by diluting the animal's own blood with one of the salt solutions.

These solutions may be arranged into two general groups : non-nutritional, or those composed wholly of inorganic salts and water ; and nutritional, or those containing, in addition to the substances found in the first group, organic substances found in the blood.

As judged by the results, solutions containing blood are in a class by themselves, while next come the solutions most nearly approaching them in composition—*e.g.*, whey solutions. Only such solutions are capable of initiating and maintaining for any considerable length of time efficient working of the mammalian heart. By efficiency of solutions in restoring the heart is meant the production of rhythmical contractions of the whole heart of sufficient force and rate to maintain a circulation equal to that normally performed, and not merely the causation of visible contraction of isolated portions of the cardiac musculature.

What has been said may also be applied to the restoration of the heart *in situ*.

Efficiency of Perfusion of the Coronary Arteries in Starting the Heart in Situ.—This is shown in Protocol I. The blood-pressure tracing taken from the common carotid artery of a dog showed that the pressure had fallen to zero (Tracing 1). It must be remembered that as a rule the heart continues to beat for some time after its force has ceased to be communicated to the manometer. This condition has in some cases been observed to extend over a period of hours, but usually it is of only a few minutes' duration. The thorax being open in this case, the heart was directly inspected, and no contraction of any part of the organ could be detected. It is well known that resuscitation is much easier to accomplish if begun while the heart is yet contracting, even though feebly (*cf.* p. 328).

Protocol I.

RESTORATION OF THE HEART IN SITU.

Young bitch ; weight, 6 kilos.

4.18 : Etherized dog ; inserted tube in trachea for artificial respiration ; tied a cannula in each of the common carotid arteries ; cut away anterior wall of thorax, exposing heart ; adjusted cardio-

FIG. 147.—TRACING 1: RESUSCITATION OF THE MAMMALIAN HEART. BLOOD-PRESSURE RECORD.

(*Interstate Medical Journal*, 1908, xv., No. 6.)

graph, and connected manometer with cannula in left common carotid artery for blood-pressure. Smoked drums were used for recording movements of the heart and blood-pressure.

4.55 : Started Tracing 1 (1).

4.58 : Began asphyxiation by stopping artificial respiration (2).

5.03 : Last gasp (4).

Oscillation of the mercury ceased between (3) to (4) on blood-pressure tracing, but contractions of the heart were recorded by the cardiograph to (5).

5.07 : 30 : At this point drums were stopped.

5.09 : Began artificial respiration, cardiac massage, started injection of 0·9 per cent. sodium chloride solution into right common carotid artery, and occluded thoracic aorta by ligature previously placed [blood-pressure tracing, (5 *a*)].

5.14 : Massage and injection discontinued (6).

5.17 : Released aorta (7). Note accompanying sudden great fall of blood-pressure.

For efficiency of recovery, compare Tracing 1 (1) to (2) (blood-pressure, 90 millimetres mercury) with Tracing 2 (1) to (2) (blood-pressure, 60 millimetres mercury).

Summary.

"Normal" blood-pressure, 60 millimetres mercury.

Period of asphyxiation, eleven minutes.

Time for complete resuscitation of heart, six minutes.

Blood-pressure thirty minutes from time of beginning of resuscitation, 90 millimetres mercury (or 50 per cent. more than before asphyxiation).

Respiratory and voluntary movements, corneal reflex, etc., were thoroughly re-established before this time.

The method employed consists of the following procedures :

Artificial respiration, which was early instituted for the purpose of oxygenating the blood in the pulmonary capillaries. In the experiment being described it was given directly with a bellows connected with a tube inserted into the trachea. In the intact

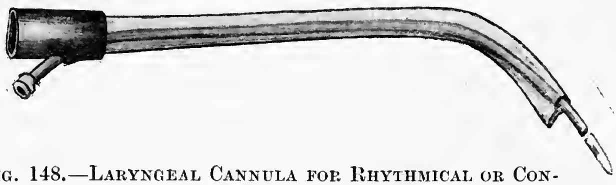


Fig. 148.—Laryngeal Cannula for Rhythmical or Continuous Pulmonary Insufflation.

animal it may be given similarly by means of a tube passed into the trachea through the larynx, or by any of the well-known methods of thoracic manipulation, such as Sylvester's or Schäfer's. Or the lungs may be ventilated by continuous insufflation. In passing, it is interesting to note that practicability of continuous pulmonary ventilation was demonstrated before the Royal Society by Robert Hooke in 1667, when he kept an animal alive for over an hour

without any respiratory movements by directing a strong blast of air down the trachea while the thorax was opened, the lungs being pricked with a fine needle to allow the escape of air; that Nagel showed that a pigeon could be kept alive without respiratory movements by sending a current of air through the opened humerus into the air sacs; and that Hans Hirsch, a pupil of Volhard, in 1905, laid the foundations of the practical application of the insufflation method, Volhard himself reporting the complete method in 1907.

Therefore, to Robert Hooke we are indebted for demonstrating the principle, and to Volhard and his pupil for making the practical application of it. The method has been widely employed, and is known as the "Volhard method."

More recently others have written on the subject.*

But to return to the experiment.

Massage of the heart was also promptly begun. This was chiefly for the purpose of establishing a pulmonary circulation before the heart had sufficiently recovered to adequately pump the blood. The establishment of the pulmonary circulation is very important, as it not only tends to relieve the tension in the right heart and great veins due to congestion, which may seriously interfere with the recovery of the heart, but also supplies oxygenated blood in the root of the aorta for admixture with the fluid used for perfusing the coronary vessels.

In the experiment under consideration the heart was directly massaged; but in the intact animal, in case of cats and dogs, this may be adequately performed by manipulation of the chest wall. In large animals with rigid thoracic walls it is sometimes advantageous to make an opening into the abdominal cavity and, by inserting the hand, manipulate the heart through the diaphragm.

Perfusion of the coronary arteries was accomplished by introducing one of the fluids previously discussed, as 0·9 per cent. sodium chloride solution, into the root of the aorta under sufficient pressure to force it, together with the blood massaged into the aorta, through the coronary arteries. In this instance the aorta was occluded just distal to the left subclavian artery by a temporary ligature (see p. 32).

In resuscitating animals with the view of bringing about complete recovery we use an instrument consisting of two tubes, one of which runs inside the other. The smaller tube is connected externally with a syringe, while internally it opens beneath a sleeve

* *Cf.* Elsberg for results on man.

of thin rubber fitted around the larger tube near the end, and tied tightly above and below around its edges. Liquid forced out of the syringe is delivered by the small tube between the rubber sleeve and the large tube, with the result that the sleeve is expanded in the form of a bulb. Before inflating the rubber sleeve the instru-

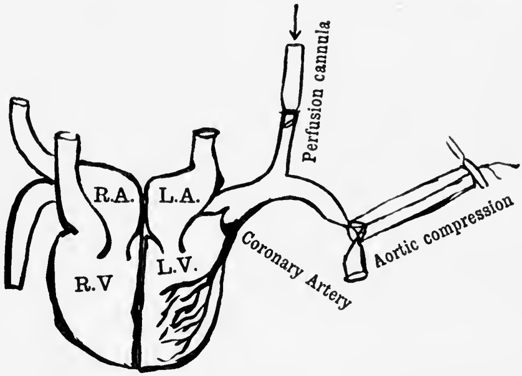


FIG. 149.—SHOWING METHOD OF PERFUSING THE CORONARY ARTERIES OF THE HEART IN SITU.

ment is pushed down one of the carotid arteries, preferably the left, and the lower end carrying the sleeve directed into the arch of the aorta towards the heart. The external end of the large tube is then connected with a pressure bottle containing the perfusion solution, and the rubber sleeve inflated by means of the syringe until the aorta is occluded. The perfusion liquid, when turned on,

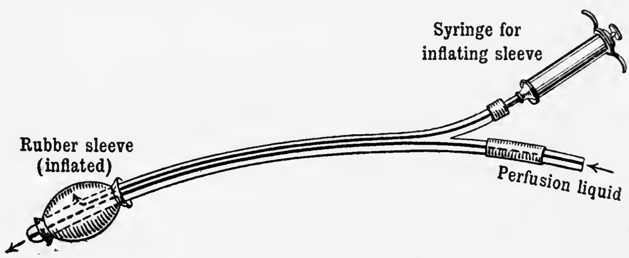


FIG. 150.—INSTRUMENT FOR PERFUSING THE MAMMALIAN HEART IN SITU.

will then escape through the open end of the large tube beyond the point of aortic occlusion, and the pressure in the root of the aorta will be raised thereby, resulting in a circulation of the liquid through the coronary arteries.

A solution of 0·9 per cent. sodium chloride was injected into the

central end of the common carotid artery at approximately body temperature, and under a pressure of 160 millimetres of mercury, which is probably not much higher than the normal arterial pressure in such an animal. As before stated, the solution was mixed with oxygenated blood forced into the root of the aorta by massage of the heart, so that in reality the coronary arteries were perfused with dilute arterial blood, which, next to whole blood, would seem to be, so far as is known, the best possible fluid for this purpose.

At the same time the brain and upper part of the spinal cord were perfused, as some of the arteries supplying these parts were not shut off. This is of extreme importance, as the cells of the central nervous system are much more susceptible to, and are more readily killed by, anæmia than the cells comprised in most of the other tissues of the body. This is well illustrated by the results obtained by the writer, with Professor Stewart and Dr. Pike.* We found that it was possible to resuscitate cats after as much as sixty minutes of complete anæmia of the upper central nervous system, but after periods of more than twenty minutes power of permanent return of normal function was apparently lost. But these experiments will be given in some detail presently.

As the heart of the animal being resuscitated began to beat efficiently (Tracing 1) cardiac massage and the injection of the solution was gradually discontinued. Next, the aorta was partially released, so that the channel of arterial circulation became widened. As a rule complete release of the aorta must be delayed until evidence of return of vasomotor function is observed, as the heart may cease to beat from lack of pressure, due to too little peripheral resistance. Return of function of the respiratory and vasomotor centres ordinarily occurs at about the same time, so that the respiratory movements furnish a good index on the state of the vasomotor centre. *Artificial respiration should be continued until the automatic respiratory movements become strong and regular*, and this point cannot be emphasized too strongly. At this time also it is safe to release the aorta completely.

Influence of Occlusion of the Aorta on the Circulation.—This is shown in Protocol II. The arteries are normally maintained in a state of tonic contraction, as before stated, by impulses that originate in the upper part of the spinal cord, and pass to the muscular fibres situated in their walls over nerves known as the "vasomotors."

* *Science*, N.S., 1905, xxi. 887 ; *Journal of Experimental Medicine*, 1906, viii. 289, 321 ; *American Journal of Physiology*, 1906, xvii. 344.

Owing to this contraction of the muscle fibres, the lumen of the vessels are narrowed, and thus increased resistance is offered to the passage of the blood into the capillaries. The arteries, therefore, are unable to empty themselves by their elastic contraction between the beats of the heart, and the arterial blood-pressure is maintained. In the animal used in this experiment, in which this mechanism was intact, the mean blood-pressure, as indicated by the manometer connected with one of the common carotid arteries, was about 90 millimetres of mercury.

Protocol II.

Maintenance of the Circulation after Decapitation.

Animal employed for resuscitation (Protocol I.) was the one utilized in this experiment. It exhibited an unusually low blood-pressure even before asphyxiation in the first case, as shown by tracings. Arrangement of apparatus same as in Protocol I.

5.39: Started Tracing 2 (1) to (2), slow speed; (2) to (3), fast speed; (3) to (4), slow speed.

5.41: Began ligating all tissues of neck, (4).

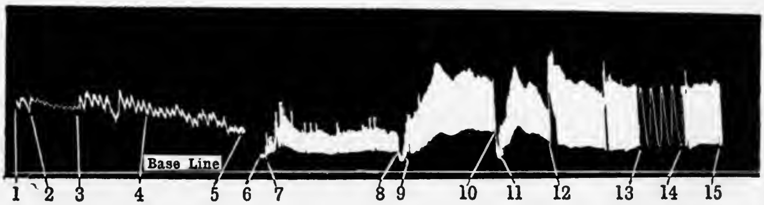


Fig. 151.—Tracing 2: Efficiency of Aortic Occlusion (and Artificial Respiration) in maintaining the Circulation after Decapitation. Blood-Pressure Record.

(*Interstate Medical Journal*, 1908, xv., No. 6.)

5.44: Sawed head completely off, (5) to (6); occluded thoracic aorta, (7) and (9) and (11).

Release of aorta is indicated by (8) and (10).

Injected sodium chloride solution.

5.55: Drum on fast speed, (13) to (14).

5.57: Drum stopped, (15).

6.09: Intrathoracic temperature, 31° C.

6.10: Started Tracing 3 (1); drum on fast speed, (2) to (3); injected more sodium chloride solution, and released aorta, (4).

Compressed aorta, (5).

Released aorta and injected sodium chloride solution, (6).

Stopped injection, (8).
Clamped aorta, (9).
Injected sodium chloride solution, (10).
Stopped injection, (11).

(Total solution injected in whole experiment less than 1 litre. Considerable blood was lost from the intercostal arteries, as these vessels were not ligated before removal of thoracic wall.)

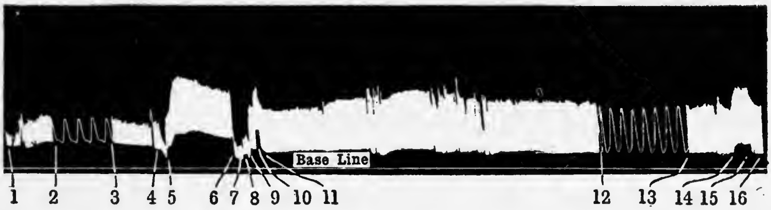


FIG. 152.—TRACING 3: MAINTENANCE OF CIRCULATION AFTER DECAPITATION BY OCCLUSION OF THE AORTA. BLOOD-PRESSURE RECORD.

(*Interstate Medical Journal*, 1908, xv., No. 6.)

NOTE.—This shows greater efficiency of injection with aortic compression than without. Also note the great difference in maximum and minimum and mean blood-pressure with and without aortic compression, being far greater in the former. The great pulsatory oscillation (maximum and minimum pressure) is probably due—

FIG. 153.—TRACING 4: EFFECT OF ASPHYXIA ON BLOOD-PRESSURE AFTER DECAPITATION. BLOOD-PRESSURE TRACING SHOWING EFFECT OF ASPHYXIATION AFTER DECAPITATION.

(*Interstate Medical Journal*, 1908, xv., No. 6.)

(1) to vaso-dilation ; (2) relative inelasticity of the vessels ; and (3) small capacity of arteries to which the circulation is restricted.

Drum on fast speed, (12) to (13).
Animal's hind-quarters elevated, (14) to (15).
6.27 : Stopped drum, (16).
6.35 : Started Tracing 4 (1).
Drum on high speed, (2) to (3).

Compressed abdomen, (4).
Released aorta, (5).
Clamped aorta, (6).
Drum on high speed, (7) to (8).
6.38 : 30 : Discontinued artificial respiration, (9).
6.46 : Oscillation of mercury ceased, (10).
7.01 : Last visible heart-beat.

The increased heart action after occlusion following temporary release of aorta in part may be explained by the stimulating action on the heart of increased pressure in coronary circulation by the increase in percentage of blood in circulating medium. It should be remembered that a considerable amount of sodium chloride solution has been injected into this animal, and since the aorta has been occluded most of the time, thorough admixture with blood may not have occurred in the vessels below the point of occlusion. Therefore, when the aorta is temporarily released, some of this blood in the great veins is forced into the active circulation, thus serving to increase the blood content of the circulating liquid. Again, it is conceivable that since the blood in the restricted circulation is not permitted to pass through the abdominal viscera, waste products may accumulate and available food products be removed, so that when the blood from the great veins is caused to enter the active circulation, these conditions may in part account for the behaviour of the heart (*cf.* note, p. 311).

Attention is called to the rise in pressure and increased heart action following the preliminary fall after cessation of artificial respiration in the decapitated animal, which is shown in Tracing 4 between (9) and (10). Whether or not a vasomotor action is concerned in this phenomenon is not yet determined.

Summary.

	Millimetres Hg.
The mean blood-pressure before decapitation was approximately	90
The maximum blood-pressure before decapitation was approximately	100
The minimum blood-pressure before decapitation was approximately	80
After decapitation, with the aorta occluded :	
Approximate mean blood-pressure	85
Approximate maximum blood-pressure	135
Approximate minimum blood-pressure	35

During periods when the aorta was released:	Millimetres Hg.
Approximate mean blood-pressure	17
Approximate maximum blood-pressure	20
Approximate minimum blood-pressure	14

After decapitation the circulation was maintained for fifty-four minutes and thirty seconds, at which time artificial respiration was discontinued and the experiment closed.

A ligature was placed around the thoracic aorta, and the two ends passed through a glass tube of convenient length and secured. By traction upon the free ends of the ligature the aorta was compressed against the end of the tube. Thus it could be occluded at will.

The tissues of the neck were ligated and divided. Variations in blood-pressure may be observed at this stage of such an experiment, due to the tying off of the blood-vessels and stimulation and division of the nerves [Tracing 2 (4 to 5)]. Immediately after division of the spinal cord and complete decapitation there was a marked lowering of the blood-pressure and disappearance of respiratory movements. Artificial respiration was then begun, and the aorta occluded by traction on the ligature previously placed. There was a sudden and great increase in blood-pressure, due to the occlusion. On releasing the aorta there was a corresponding fall in pressure [Tracing 2 (10)]. By adequate occlusion of the aorta the blood-pressure may be maintained sufficiently to keep the heart beating regularly for hours.

After decapitation vasomotor tone is lost to a large extent, and ordinarily, even though artificial respiration be given, the blood-pressure rapidly sinks to zero. By occluding the aorta, not only may the peripheral resistance be raised to normal or higher, but by restricting the vascular area the ratio of the mass of blood in the body to the capacity of the vascular system actively concerned may be increased. Therefore a better return of blood to the right heart is secured.

Resuscitation of the Circulation.

In an experimental study of resuscitation of animals after apparent death from suffocation, drowning, electrocution, anæsthetics, and the like, with Dr. G. N. Stewart, in order to discover the maximum time after which an animal could be completely resuscitated, a large series of experiments were performed upon dogs and

cats in order, among other things, to determine what methods were most efficient in restoring the circulation, and what period of complete anæmia the brain and upper part of the spinal cord may successfully withstand—that is, after what period of such anæmia may the animal be restored to a fairly normal condition. For since it was believed that the central nervous system was perhaps more susceptible and more harmfully permanently impaired by complete anæmia than other tissues of the body, by establishing the conditions of its resuscitation, we hoped to thus answer the question for the entire organism. Before the experiments were completed Dr. F. H. Pike joined us, and the papers based upon these results were largely prepared by Dr. Pike. The results are so clear-cut and of such interest to the question of general resuscitation that they will be given in some detail.*

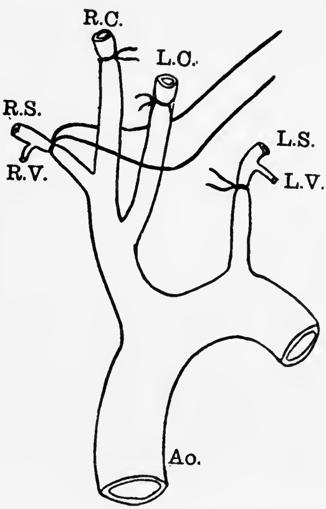


Fig. 154.—Showing Arteries occluded in producing Temporary Cerebral Anæmia.

Ao., Aorta; R.S., right subclavian; R.V., right vertebral; R.C., right carotid; L.C., left carotid; L.S., left subclavian; L.V., left vertebral.

(*Journal of Experimental Medicine*, 1906, viii. 292.)

The experiments were performed on cats and dogs. In experiments in which it was desirable to keep the animal alive some hours or days after occlusion, a glass tube, narrowed at one end, was inserted through the mouth and between the vocal cords into the larynx after ether narcosis. Ether, the only anæsthetic used, was administered through the tube. Artificial respiration was accomplished by slipping the free end of the air-tube from a tank of compressed air, with an escape-valve in the side, over the end of the glass tube, and rhythmically inflating the lungs by turning a cock on the compressed air-pipe. This was performed by an automatic device.

Through an incision in the median line in the lower part of the neck the right innominate and left subclavian arteries were secured. Acute temporary cerebral anæmia was produced by passing liga-

* A considerable portion of the matter herein presented is largely quoted from the *Journal of Experimental Medicine*, 1906, viii. 289-3 .1; 1908, x. 490-520.

tures around the innominate, and the left subclavian proximal to the origin of the vertebral artery. Traction on the ligatures produced occlusion of the arteries. The blood-pressure was always taken from the left carotid artery unless otherwise stated. Respiratory tracings were made by means of a tambour connected with the laryngeal tube.

Tests of Occlusion.—The phenomena following complete occlusion of the cerebral arteries are characteristic and constant. The nose and mucosa of the mouth become white as in death. Respiration ceases, the reflexes disappear, and the pupils dilate completely. The heart continues to beat efficiently. Intravenous injection of indigo carmine showed, on post-mortem examination of animals allowed to die without restoration of the cerebral circulation, that anæmia of the brain and medulla oblongata was complete in animals showing these symptoms. No trace of the pigment was ever found above the level of the calamus scriptorius. Usually the pigment extended no higher than the third or fourth cervical segment. One of the most striking effects of occlusion of the cerebral arteries is the rapid and great rise in blood-pressure. There is at first a rise above the general pressure before occlusion, then a fall, succeeded by a second rise and a second rapid fall to the level which is maintained, with only a very gradual fall, throughout the period of occlusion.

In the light of our results and those of previous observers we concluded that under the influence of anæmia the vaso-constrictor centre in the medulla follows in the wake of the other cephalic centres, and loses its power of functionating, but the blood-pressure is maintained at a height of 40 to 60 millimetres of mercury until the end of occlusion. It appears that blood-pressure in the trunk is maintained after the medullary centre loses its power of functionating by accessory vasomotor centres.

The pulse-rate immediately after occlusion may be increased for twenty to sixty seconds, but this is not a constant occurrence. A period of vagus inhibition follows, and with it are associated the secondary respiratory gasps, after which the inhibition gradually weakens and ceases entirely, simultaneously with the gasps, both inhibitory and respiratory centres succumbing to the anæmia at approximately the same time. The pulse-rate then increases to a maximum, after which, if the period of occlusion be sufficiently prolonged, it becomes slower until the moment of restoration of the cerebral centres. Respiratory movements continue as usual for

10 to 165 seconds, when they cease. After a pause of thirty seconds to two minutes, a secondary series of gasps of the Cheyne-Stokes type occurs. Ten seconds to a minute may elapse after occlusion before the pupil begins to dilate. The movement is rapid, four or

Fig. 155.—Showing Effect of Compression of the Cerebral Arteries upon Arterial Blood-Pressure, both Central and Distal to the Points of Occlusion, and upon Respiration.

Cannulæ in central and peripheral ends of left carotid. Base line for peripheral (cephalic) pressure first above time tracing; base line for central (cardiac) pressure second above time tracing. Curve of cephalic pressure crosses base line for pressure from central end. Respiration at top, above blood-pressure. No artificial respiration.

(*Journal of Experimental Medicine*, 1906, viii. 296.)

five seconds being sufficient time for maximal dilation.* Soon after the dilation of the pupils the cornea becomes lax, then sunken and furrowed, indicating a reduced intra-ocular pressure.

There is usually a sudden stiffening of all the muscles following occlusion, with violent movements of the fore- and hind-limbs and

* *Cf.* Guthrie, Guthrie and Ryan, *Science*, N.S., 1910, xxxi.

tail. Micturition and defæcation may occur. Then the fore-limb movements cease, shortly afterward the hind-limbs relax, and the whole animal lies limp and quiet until after the restoration of the cerebral circulation. The intravenous injection of strychnine sulphate during the period of occlusion is followed by the usual spasms of the abdominal and hind-limb muscles, but no effect, except a possible slight exaggeration of the reflexes, is observed in the forelimbs, and only when the strychnine is injected immediately after occlusion and before the period of high pressure. The anterior part of the cat may be completely relaxed and inert, while the posterior half may show violent strychnine spasms, as in the normal cat. The blood-pressure rises after the injection of strychnine. The early exaggeration of the anterior reflexes suggests the possibility of an increased flow of blood through the anastomotic channels during the period of high blood-pressure, but the subsequent complete relaxation of all anterior muscles, even when twice the minimum fatal dose of strychnine is injected, indicates that the anæmia of the anterior part of the cord is very complete.

The picture presented at the close of a typical occlusion is an animal with widely dilated pupils, lax and sunken cornea, motionless eyelids, no lacrymal secretion, no saliva, bloodless mucosa of the nose and mouth, relaxed muscles, no voluntary respiratory movements, low blood-pressure, with a heart becoming slow and weak, perhaps stopping if the occlusion be long continued.

The General Phenomena following Restoration of the Cerebral Circulation.

The empty cerebral arteries fill rapidly after removal of the ligatures. The mucosa of the nose and mouth lose their pallor, and the blood flows freely from a nick in the nasal septum. The general arterial blood-pressure falls. The pressure may even sink to zero, the heart stop, and death result.

In most cases rise in pressure succeeds the fall, continuing until the pressure before occlusion is approached or reached. Traube-Hering curves and other irregularities appear in the blood-pressure tracing. Gradually the centres apparently become more stable in function, and the irregularities disappear. Stimulation of the sciatic nerve is followed by the usual rise in pressure at this period, although it may not cause a rise in those cases where the pressure is very low and which terminate fatally.

The pulse-rate before release of the cerebral arteries may increase after the restoration of the cerebral circulation, to diminish as the time of the first respiratory gasp approaches, again increase as respiration becomes established, perhaps become very rapid, and finally, after some hours or days, return to a normal rate. After prolonged periods of anæmia, the heart may gradually stop.

The disappearance and the return of respiratory movements are more definitely marked and constant phenomena than the disappearance and return of the eye reflexes. The exact moment at which the vasomotor centre ceases to function is not so easy to determine as the time at which the respiratory centre fails, as there is no such sudden cessation of a very noticeable phenomenon connected with the former as with the latter mechanism. In such an experiment the vasomotor centre fails gradually, and the time of cessation of function is further masked by the fact that there are accessory vasomotor centres in some animals which assume a part of the function of the medullary centre on the failure of the latter. The vasomotor centre appears to be more resistant to anæmia than the respiratory centre, and to attain a certain degree of functional activity after the restoration of the cerebral circulation before the respiratory centre gives any sign of its activity. Traube-Hering curves have sometimes appeared in the blood-pressure tracing after total cessation of respiratory movements. In these experiments, it must be assumed that the vasomotor centre is the more tenacious of life. Exact observations on the order of return of function of the vasomotor and respiratory centres after restoration of the circulation following complete cessation of the general circulation are wanting.

Crile,* from observations on dogs killed by chloroform or suffocation, and resuscitated by injecting adrenalin into the circulation, believes that in general respiratory movements are resumed before vasomotor control. But not much weight can be given to this statement, as, owing to the method of resuscitation, the peripheral action of the adrenalin masks the evidence upon which the return of vasomotor control is based.

In our experience, the tonicity of the bulbar vasomotor mechanism began to return in the resuscitation period as a rule before the respiratory centre began to discharge, and, as is the case with the respiratory centre, there was often a period during which the blood-pressure might be rising, but when reflex changes in pressure did

* *Journal of Experimental Medicine*, 1908, xi. 789.

not occur through stimulation of the vagus or brachial nerves. Similarly, a time was observed in the occlusion period during which the blood-pressure was still high, and the bulbar vasomotor mechanism undoubtedly functional, when stimulation of the afferent nerves produced no effect on the blood-pressure curve.

The animal lies motionless after occlusion, with the blood-pressure gradually rising. The first sign of returning vitality in the respiratory centre is a strong gasp, followed by others, the rate being about four a minute at the outset, and gradually increasing until spontaneous respiration is established. The respiratory rate is at first usually much slower than that of a normal cat, and hours or even days may elapse before the normal rhythm is re-established. After prolonged periods of anæmia—*e.g.*, eighty-one minutes—the respiratory gasps may not occur after the release of the cerebral arteries. An occlusion of twenty-eight minutes was followed by a first gasp forty minutes after release. The gasps continued for fifteen minutes, six to eight per minute, and then ceased. Artificial respiration was continued, but dilation of the pupils, and later failure of the heart, followed. Apnœa was frequently met with following long occlusion. Respiratory gasps occurred, became almost frequent enough for spontaneous respiration, and suddenly ceased.

The closely equal susceptibilities between the vagus and the respiratory centres after occlusion has been mentioned. Pulse-counts indicate a similar connection after restoration of the cerebral circulation, a distinct cardiac slowing often occurring at the time of the first respiratory gasp. A very early sign of returning function, occurring before respiration or contraction of the pupil, is fibrillating movements of the tongue. Such movements are observed after occlusion of ten minutes or more, and continue until the other reflexes are well established. A closely related phenomenon is the twitching of the skin of various parts of the body, but especially of the shoulders and thighs. It generally appears a little later than the fibrillating movements of the tongue, and lasts about as long.

The light, lid, and corneal reflexes are inconstant. The lid and corneal reflexes may return relatively soon after release of the cerebral arteries, while the light reflex may not be demonstrable until two or three days later. None of them return after long periods of occlusion—*e.g.*, sixty minutes. The pupils do not remain contracted after failure of respiration. In cases of paralysis of the respiratory centre during anæsthesia, the pupil first

dilated to the maximum, the animal perhaps made two or three expulsive gasps, after which the respiration failed. After release of the cerebral arteries gasping respiratory movements appear before complete contraction of the pupils, but they may be narrowly contracted before respiration is fully established, and usually they remain contracted in apnœa of brief duration. It is difficult to differentiate in this condition between the action of the cerebral centre and the action of the cervical sympathetic, which, as Tuckett has shown, will withstand vastly longer periods of anæmia than the cerebral centres. Two and three days after occlusion may find the pupils widely dilated, while respiration proceeds without difficulty.

Intra-ocular pressure is re-established before, coincidently with, or more rarely after, the contraction of the pupil.

The picture presented at this stage is one in which the natural pink has replaced the deathly pallor of anæmia, the tongue is fibrillating actively, the skin twitching, pupils contracted, and respiration spontaneous, but slow. The corneal, lid, and light reflexes may be present. If the period of anæmia is prolonged, the cornea may be lax.

Convulsions, varying in severity from occasional twitchings of the limbs to extreme opisthotonos and violent struggles of tonic or clonic type, sometimes begin before the full return of the reflexes. Occasionally the cat may lie quietly for one to three hours before the convulsions begin. The head may be drawn back in extreme opisthotonos, or may be bent downward with the back convex. There may be tonic spasm of the fore-limbs and clonic spasms of the hind-limbs. Again, there may be violent clonic spasms in which the animal flings itself about from one side of the room to the other. The cat may lie quietly on its side, the head in moderate opisthotonos, the fore-legs outstretched in tonic extensor spasms, with alternate protrusion and retraction of the claws. If the head is gently pushed forward until it is in line with the long axis of the body, the flexor muscles then go into spasm, so that the tip of the nose and the hind-feet are approximated. Soon, however, the extensor muscles overcome the flexors, and opisthotonos returns. The convulsions may follow in such rapid succession as to make it difficult to distinguish any interval between successive seizures. At other times intervals of five to twenty minutes elapse between any two convulsions. The pupils dilate widely during the spasms. Respiration may be impeded during the spasms and rapid during

the intervals. Attempts at vocalization are confined as a rule to the intervals between convulsions. Stroking the fur, clapping the hands together near the animal's ears, walking across the floor, passing a thermometer bulb into the rectum, and even blowing gently across the fur, may throw the animal into spasms. The period of frequent and violent spasms lasts two or three hours to as many days.

Micturition and defæcation occur as usual during this period. In all cases in which urine voided after occlusion has been examined, it has been dextro-rotatory, and contained a reducing substance. In one experiment, three samples of urine voided two hours and twenty minutes, three hours and thirty minutes, and twenty hours respectively, after the beginning of occlusion showed the highest percentage of reducing substance in the second sample. A very slight fermentation occurs with yeast, but not at all proportional to the amount of reducing substance present.

The temperature is often subnormal, and may not rise to normal for several hours or even days. It appeared at times that a high temperature may increase the severity of the spasms, while a reduction of the temperature by putting the cat in the ice-box may reduce their severity, but of this we were not sure. The presence of a cloth covering in which the animal can entangle itself increases the severity of the spasms, as the struggles continue until the covering is thrown off. The most successful treatment consisted in keeping the animal as quiet as possible, covering it when practicable to do so without increasing the spasms, but relying mainly upon perfect quiet and freedom from jar. Ether and chloral will stop the spasms, but may stop respiration and heart-beat also. Seizing the feet and stretching the limbs subdue the spasms during the several seconds that the limbs are held.

Severe convulsions may terminate in death twelve to thirty hours after their onset. The condition of the brain and anterior part of the cord at the end of occlusion is such as to allow of no reflexes. Fifty-two minutes after release, following an occlusion of fourteen minutes, there was no response of the anterior part of the cord to the intravenous injections of strychnine. There was no response twenty minutes after release following an occlusion of seven minutes. Strychnine at this time appeared to retard rather than accelerate the recovery of function by the anterior part of the cord. Severe strychnine spasms of the posterior half of the body followed the subcutaneous injection of strychnine, after the return

of respiration and eye reflexes thirty-three minutes after release from an eight-minute occlusion, but the anterior half of the body was relaxed. Seven hours after release from an occlusion of eight minutes the anterior part of the cord had regained its irritability to strychnine. General spasms appeared, stronger in the hind- than in the fore-limbs. On increasing the strychnine, the fore-limbs relaxed before death, while the hind-limbs were still in spasm.

The first reflex response to pulling or pinching the fore-legs occurs in the leg of the same side. Later, striking one fore-leg causes reflex movements of both.

The Deportment of the Animal in the Post-Convulsive Period.

Strictly speaking, there is no post-convulsive period except in those animals which recover completely. For convenience of description, we may speak of the period after cessation of the frequent and violent spasms as the post-convulsive period. It is characterized by infrequency or total absence of convulsions. There are three phases : (1) Complete recovery ; (2) partial recovery ; and (3) death.

The phenomena observed are shown in the following protocols :

Complete Recovery.

Very large male cat. Ether; intubation; occlusion of eight minutes. Pupils dilated completely in twenty seconds, and cornea became lax. Respiration ceased in seventy seconds; first respiratory gasps after release of cerebral arteries in eight minutes; pupils contracted in fourteen minutes; natural respiration in eighteen minutes. Unusually severe spasms began twenty-nine minutes after release, and lasted one hour. The cat was then able to crawl about, but unable to stand because of paralysis of fore-limbs. Paralysis and wrist-drop were entirely gone the next morning (twenty hours after release). A peculiar drooping attitude was maintained for two days; afterward the cat appeared entirely normal in every way. When killed by chloroform narcosis three months later, the lungs showed nodular thickenings and some inflation.* No gross changes in brain.

Complete recovery has resulted after occlusion of five, six, eight, nine and five-sixths, and sixteen and a half minutes.

* Pulmonary changes are probably due, in part at least, to artificial respiration (C. C. G.).

Partial Recovery.

The most interesting case of all comes in this group. Adult female cat in advanced pregnancy. Ether; intubation; occlusion of ten minutes; pupils dilated in fifteen seconds; last respiration in thirty seconds; first respiratory gasps eleven minutes after release; spontaneous respiration in twenty minutes; pupils contracted in twenty-four minutes; corneal reflex present in ninety minutes. Convulsions began one hour after release of cerebral vessels. Extreme opisthotonos and violent clonic spasms never appeared, but convulsive movements of the limbs were present, without any intermissions, for three and a half days. Cat lay on her side all the time. Violent spasms resulted whenever the fur was stroked. Walking across the floor caused convulsive starts. The click of a stop-watch near her ear, blowing against the fur, or any other slight disturbance, caused a convulsive start. The pupils were wide, with light reflex appearing the second day.

On the morning of the fourth day she was found in a half-sitting posture, head drawn back, and fore-paws outstretched. On the morning of the sixth day she was able to stand and walk clumsily. Paralysis of limb muscles, but no wrist-drop. She cleaned her paws, purred when spoken to or stroked; lapped water and milk for the first time since occlusion; had been fed previously by passing water or milk into her mouth through a tube.

Seventh Day.—Walked in a circle, bumping against bars of cage. When placed on floor of room walked in circle, the size of which was independent of chairs or tables in the way. Bumped into objects, probably not because of blindness, but lack of control of movements. When put in a clear space she walked in a circle as before, going two or three times in the same path, as shown by the marks of her fore-feet, which were dipped in water. Little change in deportment in succeeding days.

Twelfth Day.—Four kittens were born in the morning. One dead when first seen. Others apparently as vigorous as kittens of a normal mother. Old cat paid no attention to them; apparently totally ignorant of their presence if a few inches away, though they mewed loudly. If a kitten came near enough to touch her nose, she licked it with her tongue, fondled it with her paws when nursing, very much as a normal cat would. If a kitten wandered away, she seemed totally unconscious of its existence, and made no effort to bring it back.

Fourteenth Day.—Light reflex present in some degree. Cat appeared blind, not closing her eyelids until the eyeball was touched. Refused to walk when placed upon the floor. Mewed loudly much of the time, and nothing seemed to pacify her. Appeared deaf to ordinary sounds, but total deafness was doubtful.

Fifteenth Day.—Death by inhalation of chloroform because of puerperal infection. Brain and cord showed no gross lesions on post-mortem examination. A considerable quantity of fat present in omentum and mesentery. Stomach contained undigested meat.

Three stages could be distinguished—a period in which all reflexes, with possible exception of the light reflex, were present; a prolonged period of convulsions; and a period marked by the loss of intelligence.

Partial recovery, with paralysis of one fore-leg, and death from accidental strangulation on the ninth day, resulted from an occlusion of eight minutes. There were occasional convulsions, following unusually violent attempts to move about in the later period, but there was no loss of intelligence. Another occlusion of twenty-two minutes was followed by paralysis of one fore-leg, but no observable loss of intelligence. Death from pneumonia on the seventh day.

Death.

After long occlusions, death generally follows in thirty hours, or less. No post-convulsive period appears to exist in such cases. One peculiar case comes in this group.

Occlusion, twenty minutes; symptoms of dementia appeared the third day; pupils wide and staring; choreic movements of the head. Strong tonic or clonic convulsions followed any attempt at quick or unusual movement. Cat mewed loudly when anyone came in sight. Would not eat voluntarily; scratched when milk was passed into her mouth through a tube, but swallowed some of it. Sniffed at a piece of meat held in front of her, but ate none of it. The dementia passed away. On the fifth day cat ate normally, responded to a call, and held head out to be stroked. Convulsions still followed any complicated or rapid movement. Slow movements were fairly well executed. Kept under observation nine days. Future deportment and circumstances of death, which occurred about ten days later, unknown.

Pike and Gomez studied the cytological changes in the nervous

tissues of such animals, and they summarize their observations as follows:*

"With the return of the circulation, dilation of the pericellular lymph space and slight swelling of the cell body occurs, disappearing as recovery progresses. Chromatolysis, as evidenced by poor affinity for stains, clumping, diffuse staining, and breaking into dustlike particles, induced by anæmia, is not necessarily fatal. Death of the cell is not shown histologically when tissue is removed and fixed immediately after the experiment. Some time must elapse for the detection of the vacuolation, displacement of the nucleus, and solution of the chromatic substance, indicative of profound changes. Neurones from different regions, as well as neurones of the same region, differ in degree of resistance to anæmia. The small pyramidal cells are the most susceptible, and then come the Purkinje cells, cells of the medulla oblongata, retina, cervical cord, lumbar cord, spinal ganglia, and, most resistant of all, the sympathetic ganglia cells. Failure to resuscitate animals after anæmia of the central nervous system is probably due to the destruction of many of the vital centres (vasomotor and respiratory), which do not have histological peculiarities by which they may be defined. Death, however, of a few cells of any centre does not necessarily mean the total loss of function of that centre, since the remaining cells may be sufficient to discharge the function of the centre.

Resuscitation after Stoppage of the Heart.

In attempting the resuscitation of an animal, we tacitly assumed† that no organ or system or constituent of the body absolutely essential to life had suffered irreparable injury. It would be hopeless to attempt a permanent resuscitation after the blood had clotted in the head or great vessels, or after putrefactive bacteria and other injurious organisms had entered into it in sufficient numbers to be fatal, or after the blood had been destroyed by chemicals or venom, or had suffered such spontaneous changes as rendered it incapable of aiding in the resuscitation of the tissues or of nourishing them normally after they were resuscitated.

It is manifestly impossible to tell the exact moment of clotting of the blood within the heart unless the wall of one of the cavities

* *Journal of Experimental Medicine*, 1909, xi. 257.
† *Ibid.*, 1908, x. 384.

is incised. After incision, the liberated kinase from the tissues of the heart will so hasten coagulation that the result obtained cannot be taken as the true time of coagulation. The most trustworthy results will therefore be those in which the condition of the blood within the heart is stated exactly as it is found on incision of the ventricles. The results of some observations to determine the time of intravascular clotting are given in the form of a table, showing the condition of the blood in the cavities of the heart on incision at varying intervals after death.*

TABLE SHOWING TIME OF POST-MORTEM INTRAVASCULAR COAGULATION.

Animal.	Manner of Death.	Time after Death at which Heart was opened.	Condition of Blood in Heart when opened.
		Minutes.	
1. Dog.. ..	Asphyxia after ether	100	Moderately firm clots.
2. Dog.. ..	Heart stopped from ether	21	No clot.
3. Young dog	Asphyxia after ether	30	No clot.
4. Young dog	,, ,, ,,	25	No clot.
5. Pup.. ..	,, ,, ,,	31	No clot.
6. Dog.. ..	Hæmorrhage and asphyxia	115	Clot.
7. Dog.. ..	Asphyxia after ether	130	Clot.
8. Pup.. ..	Chloroform	60	Clot.
9. Pup.. ..	,,	120	Clot in right heart; none in left.
10. Dog.. ..	,,	36	Small clot in right ventricle; none in other cavities.
11. Young dog	,,	40	No clot.
12. Dog.. ..	,,	50	Moderate coagulation in right ventricle; clot in left ventricle.
13. Young dog	,,	49	Clot.
14. Dog.. ..	Hæmorrhage and asphyxia	60	Clot.
15. Young dog	Asphyxia after ether	23	No clot.
16. Dog.. ..	Anæsthesia	176	Clot.
17. Dog.. ..	Hæmorrhage and asphyxia	153	Clot.
18. Young dog	Asphyxia after ether	40	Partial coagulation in right ventricle, but no clot in left ventricle.

The dogs on which the observations were made had been used by students for experiments on the submaxillary gland, including stimulation of the chorda tympani nerve. In some cases a certain amount of dissection was done on the abdomen after death, such as removal of the stomach. The operative procedures had un-

* *Journal of Experimental Medicine*, 1908, x. 385.

doubtedly liberated a considerable amount of kinase from the tissues. Although the early occurrence of clots was probably favoured by the ante-mortem treatment of the animals, the interval during which the blood remained unclotted is greater than the period after cessation of the circulation, after which the central nervous system can be resuscitated. Intravascular clotting cannot practically be considered a barrier to resuscitation.

The results indicate that intravascular clotting begins in the right ventricle as a rule, and that under the conditions of the examination mentioned it does not occur under thirty-six minutes, but it may be delayed for a longer time. It would seem, therefore, that under thirty minutes clotting probably does not occur in death from asphyxiation or similar means without mutilation. It should be noted, however, that of three dogs, examined by Professor Sollmann, clots were observed in the cavities of the heart of two of them twenty minutes after death.

The presence of a clot in the ventricle is probably not in itself an absolute bar to the resuscitation of the heart. The left heart seldom contains much blood after death, and a clot found in its cavities would not, in general, completely fill them, and thus prevent the inflow of blood into these cavities. And, again, the mere presence of clots, acting solely as foreign bodies in the ventricle, would present no great difficulty, as the introduction of sounds and catheters into the cavities of the heart for the measurement of endocardial pressure is a matter of common occurrence. Ante-mortem clots are occasionally found within the heart, and do not seriously embarrass its action. In starting the heart by the intra-arterial injections of fluid, the injected fluid does not necessarily enter the heart cavities at first, but goes into the coronary arteries, and reaches the cavities of the heart only after passing through these vessels.

Though perhaps not impossible, permanent resuscitation of an animal after formation of clots in the heart is hardly probable.

The time when micro-organisms may pass into the blood from the alimentary canal is of interest in this connection. In four to six hours after death some of the common organisms of the intestines are to be found in the neighbouring tissues, unless the cadaver has been put into a refrigerator immediately after death. This period, however, greatly exceeds that within which we may hope for resuscitation of the central nervous system, and is, therefore, not a consideration of great practical importance.

As the necessary condition for the resuscitation of the tissues is an adequate supply of blood, the question presents itself whether its own previously stagnant blood is the best circulating medium, or whether it might be improved by the addition of artificial liquids, or of blood from a normal animal of the same species. In general, unless blood has been lost or suffered alteration, as in carbon monoxide poisoning, the animal's own blood is adequate.

Owing to its obvious importance in the resuscitation of the entire animal, the resuscitation of the heart was studied more extensively, with the exception of the central nervous system, than any other organ or system. As it was found that certain influences and modes of death are more injurious to the heart than others, thus rendering resuscitation of the animal more difficult, the various modes of death will be separately considered.

In such experiments it is very necessary to determine accurately when the heart ceases to beat. The cessation of the oscillations of a mercurial manometer, or the failure of the carotid or other pulse, is an uncertain means of determining whether or not the heart has stopped. In these experiments the heart was exposed freely, so that the base was easily visible, but mechanical cardiac stimulation was carefully avoided. The length of time elapsing between the cessation of the external pulse and the complete stoppage of the heart is given under the various modes of causing the death of the animals.

We studied resuscitation more in detail after death from asphyxia, drowning, etc., than resuscitation after other forms of death; but in general we may say that resuscitation appears to be easier after asphyxiation than after other modes of death. Resuscitation after hæmorrhage and anæsthesia is as a rule more difficult than after asphyxia alone. In order of increasing difficulty of resuscitation we rank the forms of death as asphyxia, anæsthesia, hæmorrhage, and electrocution by the action of induced currents upon the heart.

In nearly all cases asphyxiation was produced by clamping the trachea of the etherized animal. In such an experiment the blood-pressure falls to zero, plus the residual pressure, within three to five minutes after the trachea is closed, and no oscillation can be detected in a mercury manometer connected with the carotid. On direct inspection, the auricles, and more particularly the right auricle, may be seen to beat for five to ten minutes or longer.

In two experiments a piece of sheet-rubber was tied firmly over the nose and mouth of the anæsthetized animal.

Drowning was accomplished by immersing the head of the anæsthetized animal in water.

Hæmorrhage was sometimes allowed to occur in case of asphyxia, and invariably rendered resuscitation more difficult than after asphyxia alone.

Resuscitation of the heart, by direct or intrathoracic massage, as shown by the increase of blood-pressure, and the relative certainty with which the heart started to beat, was more efficient than other forms of massage. The heart may be started ten or fifteen minutes, or even longer, after cessation of the external pulse. When the aorta is occluded, so as to confine the circulating blood to the anterior part of the animal, we have obtained resuscitation of cats as late as forty-four minutes after cessation of the external pulse.

The prompt recovery of the heart, as a result of direct massage after clamping the aorta, is shown in the following experiment, in which the heart failed during occlusion of the cerebral arteries.

Direct Massage.

Cat. Ether.

11.28 a.m. : Occluded head arteries.

11.40 : 45 : Released head arteries ; gave ether, as animal was apparently conscious. Soon after this animal stopped breathing ; heart could not be felt. There was certainly no circulation in the brain for from fifteen to twenty minutes, and no respiration after the heart failed. Opened chest, clamped aorta and started artificial respiration.

12.05 : Heart started again by massage ; artificial respiration kept up. Heart massage continued at intervals when heart needed it, compression of ventricles being made at the moment when they were felt to be commencing their contraction. Soon massage was unnecessary.

12.20 : Pupils still at maximum dilation ; eyes wide open ; no reflex ; heart beating well.

12.25 : Lacrymal secretion ; pupils somewhat smaller.

12.43 : Cat gasping ; pupils distinctly smaller.

Extrathoracic massage by rhythmical compression of the thorax over the heart by means of the hands has given fairly good results in certain stages of the heart stoppage ; but the time when such massage is effective is limited, to make the method a sure one.

Rhythmical compression of the thorax is efficient up to from three to five minutes after the cessation of the external pulse, but it is probable that in every case of successful resuscitation by this method the heart has not entirely ceased beating. Where we have been sure that the heart has actually stopped, extrathoracic massage alone has proved unsuccessful.

The degree of efficiency of extrathoracic massage in favourable cases is shown by the following experiment :

Cat. Ether ; tube in larynx.

11.59 a.m. : Occluded head arteries.

12.04 : 50 : Natural respiration stopped ; no gasps after this.

12.05 : 15 : Released head arteries ; heart beating well.

12.08 : 20 : Gasps began.

12.14 : No light, lid, corneal, or ear reflex ; tube slipped out of larynx ; respiration interrupted for three minutes. At end of that time the pupils were at maximum dilation. Massaged heart through chest wall ; no heart-beat could be felt ; cat seemed dead ; continued massage.

12.25 : 20 : Heart now felt for the first time ; artificial respiration interrupted until 12.26.

12.26 : Artificial respiration was again started ; massage of chest continued uninterruptedly.

12.28 : Heart now beating well.

Often after extrathoracic massage has failed to start the heart direct massage has proved effective. This is shown in the following experiment :

Large adult male cat. Ether ; tube in larynx ; paralysis of respiratory centre from ether ; artificial respiration started without result.

2.18 : Heart could not be felt ; no pulse in carotid (exposed in neck wound) ; pupils widely dilated ; all reflexes gone. Kept up vigorous cardiac massage through the chest wall for twenty-two minutes, elevating hind-end of animal, and trying to compress abdominal aorta with the hand through the abdominal wall. (Compression tried after massage had been continued for ten minutes without result.) No return of the heart-beat occurred ; no pulse visible in the carotid. Artificial respiration had been kept up all the time.

2.40 : Opened chest, clamped aorta, and massaged heart directly. It soon began to beat, but not very strongly. After a little time

the ventricles began to fibrillate, while the auricles still beat fairly well.

2.42 : 30 : Pupils have become somewhat smaller.

2.45 : 30 : Heart beating fairly well, although not so well as in most of the previous similar experiments. The fibrillary contractions are gone. (The abdomen had been opened at the same time that the aorta was clamped, and the intestines, kidneys, and other viscera freely manipulated.)

3.08 : Heart, which had become very weak—*e.g.*, the ventricles beating only once for two auricular beats—was restored by massage, and is now beating well.

3.31 : First movement seen—viz., twitching of the skin over right shoulder.

In endeavouring to resuscitate the heart by intravenous and intra-arterial injections, the results following injection of 0·9 per cent. sodium chloride solution, or Locke's solution, into the carotid artery or jugular vein, were disappointing. The heart remains as immobile as before, or fibrillates a little before going into rigor. The injected fluid slowly but surely distends the right auricle if injected into a vein, and escapes into the peritoneal cavity and also into the lungs, giving rise to pulmonary œdema, which would, in itself, prove fatal. But quite apart from the œdema or the occasional rigor produced in the ventricles, the presence in the vessel of such a great quantity of fluid as is usually injected would be likely to overtax the heart, even if it began to beat. Indiscriminate and unconfined injections of fluid are, therefore, worse than useless.

The fluids best adapted for injection are defibrinated blood and serum diluted with one to five volumes of 0·9 per cent. sodium chloride solution. There is much less œdema when the blood and its dilutions are used than when the fluids containing the inorganic salts alone, or with the addition of dextrose, are employed for injection.

In order to restore the circulation, adrenalin and supra-renal extract solutions have been injected in resuscitation experiments by a number of workers. Adrenalin is of slight value in cases where the thoracic aorta is occluded, unless massage is also used. With massage, when employed without occlusion of the thoracic aorta, adrenalin is of considerable value. Care must be taken not to use excessive quantities of the adrenalin, in order to avoid overstimulation of the heart and consequent fibrillary contractions.

An early experiment on adrenalin shows the uselessness of

unconfined injections, even when adrenalin is added, and the impotency of adrenalin chloride itself in starting the heart under certain conditions.

Dog: weight, 16 pounds. Given 8 c.c. of 0·2 per cent. morphine sulphate solution.*

3.15 p.m.: Anæsthetized with A.C.E. mixture; tracheotomy.

3.25: Drew off 100 c.c. of blood; connected manometers with carotid artery and external jugular vein.

3.55: Arterial pressure good; pressure in right external jugular at base line negative; began opening chest.

4.01: Artificial respiration; stimulated heart directly with induced current one minute; marked fibrillary contractions result.

4.05: Respiratory movements still persist.

4.07: No pulse visible; respiration ceased.

4.08: Heart still fibrillating; applied adrenalin on surface.

4.14: Artificial respiration; injected 10 c.c. of a mixture of 100 c.c., 0·9 per cent. sodium chloride solution, and 1 c.c. of 1 to 1,000 adrenalin chloride solution.

4.15: Heart still fibrillating.

4.16: 10 c.c. adrenalin solution injected.

4.17: 10 c.c. adrenalin solution injected.

4.18: Pressure unchanged in jugular vein; injected 10 c.c. adrenalin solution.

4.19: 42 c.c. adrenalin solution injected; ran in with very little pressure.

4.22: Pulse 130 a minute and feeble.

4.26: Stopped artificial respiration.

4.37: Injected 250 c.c. adrenalin solution.

4.39: Fibrillation of heart still feeble; no indication of rigor. Experiment discontinued.

Crile has since successfully resuscitated animals after short periods of clinical death by intravenous injections of adrenalin solution combined with cardial massage and artificial respiration;† Herlitzka has resuscitated rabbits by intra-aortic injections of adrenalin solutions. To reduce the pressure in the right auricle, blood was withdrawn through a cannula introduced into it through the right jugular vein. Under these conditions Herlitzka says that the path of least resistance lies through the coronary vessels rather than through the systemic circulation, to the right auricle.

* Experiment performed November 10, 1902, by C. C. G.

† *Journal of Experimental Medicine*, 1906, viii. 713.

The heart, as a consequence of the establishment of the coronary circulation, begins to beat.

Digitalein, which we used in rabbits only, gave results similar to those following the administration of adrenalin. The effect was more enduring than that of adrenalin, and the drug seemed, therefore, to be better adapted to the purpose.

Barium chloride was employed in a few experiments, but was abandoned as too dangerous and too uncertain.

Drugs introduced into the circulation can act upon the heart only when carried to it in the blood-stream. It is obviously useless, therefore, to try to start a heart which has stopped by subcutaneous injections of drugs. The addition of drugs which have a local action on the heart, to fluids injected into the aorta, may well have a beneficial effect. In case of the quiescent heart drugs which may beneficially affect the heart directly through its central nervous mechanism—*e.g.*, accelerator mechanism, or indirectly by raising peripheral vascular resistance—can only exert their action if cardiac massage is combined with injection of fluid containing the drugs. Adrenalin chloride, or other drugs which will constrict the arterioles, will be of service in increasing the arterial pressure and filling the coronary vessels.

In cases of hæmorrhage bandaging the limbs and abdomen, and particularly the latter, is of considerable value, owing to the initial increase in the return of the blood to the heart. But such bandaging is of doubtful value where there has been no hæmorrhage. When the blood volume is diminished, it is relatively easy to produce over-distension and standstill of the right auricle by increasing the return of blood to it. Of course, the diminution in the total vascular capacity tends to raise the blood-pressure. The maximum increase in pressure produced by any ordinary bandaging is, of course, distinctly less than that produced by compression of the aorta.

The position of the body is of importance, particularly where massage alone without intravascular injection is employed. We have thought that the advantage which experiment has clearly shown to be connected with the left lateral position, might be associated with the easier return of the blood to the heart, and possibly with a more favourable position of the ventricles for massage. The optimum position as a rule is attained by placing the animal on the left side, and slightly elevating the posterior part of the body. When there has been no hæmorrhage, too great elevation of the

posterior part of the body may easily cause over-distension of the right auricle, and make resuscitation more difficult. In a number of experiments, increase of venous pressure, corresponding to from 25 to 75 millimetres of blood, was sufficient to stop the right auricle. In one experiment closing the outflow tube in the inferior vena cava stopped the auricular beats without affecting the rhythm of the superior vena cava.

In general, the mechanical methods for raising blood-pressure are more certain and more easily controlled than the methods involving the use of drugs. It has been shown by Stewart* that stimulation of the augmentor nerves in the frog is capable of rousing the completely quiescent heart from standstill. Hering† has stated that rhythmical beats of the quiescent mammalian heart can be caused by stimulation of the nervi accelerantes. We often observed beats in the hearts of cats and dogs from mechanical and electrical stimulation of the stellate ganglion or accelerator fibres ; but we have not been able to cause complete resuscitation or restoration and maintenance of blood-pressure, which is a necessary condition for complete resuscitation, by stimulation of the accelerators alone.

The following two condensed protocols of experiments show the effect of mechanical stimulation of the accelerators. In the first there can be little doubt that the heart had entirely ceased beating before the autopsy was made. Moreover, if such beats had persisted, they would have been noticed while the chest was open and the heart exposed. This experiment demonstrates that the heart may be caused to beat by stimulation of the accelerators after it has become completely quiescent.

Cat. Occlusion of cerebral arteries for twelve minutes. Cerebral circulation restored at 11.56 a.m.; Spinal cord cut during anæmia. Artificial respiration maintained until 1.10 p.m. No spontaneous gasps occurred as long as cat was watched. Soon the animal presented every indication of death. No heart-beat perceptible; no respiration. Autopsy at 2.25 p.m. While stripping fascia and pleura from cephalic vessels, the right auricle made one vigorous contraction. It beat again when the edge of it was pinched with the forceps. Five beats were obtained by pulling at the fascia at some distance from the heart. Further attempts were not made. The ventricles did not contract.

The second experiment shows more specifically than the first

* *Journal of Physiology*, 1893, xiii. 125. For other references see Stewart, *American Journal of Physiology*, 1907, xx. 420.

† *Archiv f. d. Gesam. Physiologie*, 1906, cxv. 354.

the effects of mechanical stimulation of the accelerators, and the effect in this case extended to the ventricles as well as the auricles.

Large adult cat. Killed by etherizing and bleeding at 3.45 p.m. Heart *in situ*. Artificial respiration employed; pulmonary circulation left open.

4.00: Mixture of one-third defibrinated blood and two-thirds 0·9 per cent. sodium chloride solution injected into the aorta; auricles soon began to beat. The heart beat for a time, then ceased entirely, or went into fibrillary contractions.

4.19: Heart completely quiet. Pinching stellate ganglion of either right or left side causes a beat of the left auricle and ventricle. Right ventricle not observed. A separate beat follows every pinch.

As to electrical stimulation, the possibility of thus maintaining the heart-beat and blood-pressure must be admitted, and the work of Floresco may lead to important applications in the future. The work of Matthews and Jackson on the electrical excitation of the heart in standstill produced by magnesium salts, and of Floresco in standstill produced by asphyxia, show the possibility of using this method in practical resuscitation, and is worthy of further investigation.

A troublesome feature of resuscitation of the heart is the fibrillary contractions which often appear as a sequel of massage or intra-arterial injections. Magrath and Kennedy state that they have repeatedly seen the heart of a cat recover from fibrillation after being in that condition for many minutes. D'Halluin successfully added potassium chloride to the injected blood or other fluid to overcome the fibrillation of the heart. Herlitzka in some cases used adrenalin chloride for this purpose, with considerable success.

In experiments on the excised heart, where injection was made directly into the coronary artery, little difficulty was experienced with fibrillation. Fibrillary contractions during massage of the heart *in situ* frequently occurred, but they ceased if massage was continued, and a sufficient blood-pressure attained. For example, in one experiment fibrillation of the ventricles occurred after starting the heart by direct massage, but disappeared as the massage was continued from time to time and the blood-pressure increased. Sometimes it was impossible to get the heart to beat regularly after the fibrillations had once begun. These fibrillary contractions and other irregularities of rhythm seem as a rule more likely to occur when the salt solutions—*e.g.*, Locke's—are employed for injection or perfusion than when a proteid containing fluid,

such as defibrinated blood, dilute serum, or even a milk whey preparation, is used. The most successful means of overcoming these contractions was an adequate circulation of the blood through the coronary vessels.

The following experiment shows that recovery from fibrillary contractions may occur suddenly:

Adult male cat. Ether: tube in larynx: occlusion of twenty-one minutes. The heart stopped about sixteen minutes after the release of the arteries. Massage of the chest was tried, but to no purpose. About fifteen minutes after the heart stopped the thorax was opened, the aorta clamped, and the heart massaged directly. Heart entirely motionless at the time the chest was opened. In five minutes the auricles were beating well, and the ventricles fibrillating. The auricles began to beat very soon after massage was begun, but the ventricles not for some time. Suddenly, seven minutes after the chest was opened, the ventricles began to beat well. No further massage was needed throughout the experiment, which was continued for five hours longer. When it was discontinued, the heart was still beating well.

The question arises whether the cardiac regulative mechanisms are resuscitated at the same time as the automatic beat. In general the central innervation of the heart, both accelerator and inhibitory, appears to be in abeyance for a longer or shorter period after the spontaneous beat of the heart has been restored, the length of this period depending on the time of occlusion. The same seems to be true of the local regulative mechanism (Guthrie and Pike). For example, while in the normal heart the rate is diminished by increase of coronary pressure and increased by diminution of pressure in the heart, during resuscitation there is a period when increase of pressure is accompanied by increase in the rate, and *vice versa*, just as happens in the excised heart. This fact suggests that the local mechanism which, in the normal heart even in the absence of extrinsic innervation, causes the response of diminished rate to increased pressure and increased rate to diminished pressure, has not yet been restored. After long periods of asphyxia no restoration may take place. As regards the mechanism, whatever it may be which normally co-ordinates the contraction of the two ventricles and renders it synchronous, it seems to be resuscitated as soon as the power of the ventricles to beat is regained. For when the ventricular beat appears it is found to start synchronously on the two sides.

Arythmia of auricles and ventricles was a fairly common phenomenon in the resuscitation of the heart *in situ*, or in perfusion of the excised heart. Also arythmia of the superior vena cava and the auricles was observed.

In many of the experiments, during the resuscitation following cerebral anæmia, the heart beat as fast as hearts whose vagi have been cut, although stimulation of the peripheral end of the vagus stopped or slowed them. This may indicate that the vagus centre had not recovered its tone, although its endings were intact. During the inactivity of the vagus centre, however, asphyxial slowing of the heart occurs as usual. Since we had shown that asphyxial slowing of the heart might result after section of both vagi and division of the cervical spinal cord, it seemed that the action was probably local.

A double beat frequently occurs at a certain stage in the occlusion period, as is shown in the following experiment :

Adult male cat. Ether ; tube in larynx : pulse (under ether anæsthesia before experiment) 207 a minute ; respiration about 60 a minute.

2.50 : 00 p.m. : Occluded head arteries in usual way.
2.50 : 15 : Respiration rapid and shallow.
2.50 : 25 : Corneal reflex gone.
2.50 : 40 : Natural respiration stopped ; started artificial respiration.
2.51 : 45 : Pupils same as before occlusion, not at all dilated.
2.52 : 30 : Pupils dilating.
2.53 : 00 : A gasp (secondary series).
2.53 : 20 : Pulse had double beat usually seen at this stage.
2.53 : 30 : Pulse 216 a minute.
2.54 : 05 : Double beat of pulse gone.
2.54 : 30 : Gasps continue.
2.57 : 30 : Gasps cease ; pupils at maximum dilation.

From a study of the above, it will be seen that the double beat appears only during the time in which the cardiac and other bulbar centres remain active, and that it ceases at about the time that the inhibitory centre fails. Since the heart goes on with machine-like regularity after the total failure of the bulbar centres, there seems little doubt that the double beat is caused, in the case of the heart *in situ*, by the extrinsic cardiac nervous mechanism, and since, furthermore, it appears during the time of

the activity of the inhibitory mechanism, it is possible that this double beat is a phenomenon of inhibition.

The experiments indicated that chloroform had the most deleterious action and ether the least of the general anæsthetics employed. All the evidence tended to corroborate the current statement that chloroform acts very injuriously on the heart tissue. Morphine, when used subcutaneously in addition to any of the other anæsthetics, tended as a rule to render resuscitation more difficult. Also, the same was true after hæmorrhage.

One cause of the greater difficulty of resuscitation attending death from hæmorrhage is the absence of a sufficient volume of circulatory fluid. So first a certain volume of fluid of a suitable nature must be supplied. A fluid as good as serum or blood can only be obtained by transfusion.

Direct stimulation of the heart with induced currents caused delirium cordis. The restoration of the circulation afterward was not very successful, owing to the difficulty of overcoming the delirium. Cold, asphyxia, and the methods generally recommended for the purpose, were quite inefficient in our hands. Resuscitation appeared more difficult than after asphyxia, anæsthetics, or hæmorrhage.

Crile investigated this subject, using high tension currents. The results of resuscitation were less satisfactory than the results obtained by the same resuscitatory methods applied to animals after death from other causes, as anæsthesia.

Summary and Conclusion.

The cerebral circulation was interrupted for periods of three to eighty-one minutes by occlusion of the innominate and left subclavian arteries proximal to the origin of the vertebrals, in ninety-three cats. Eleven dogs were used in the earlier experiments.

Death, without any return of the reflexes after release of the cerebral arteries, followed an occlusion of seven and a half minutes. Respiration returned after an occlusion of one hour. Five animals have recovered completely after an occlusion of seven minutes or more. Only one animal recovered completely after an occlusion of fifteen minutes. No animal recovered completely after an occlusion of twenty minutes.

In Herzen's resuscitation of an animal after several hours of cerebral anæmia there must have been some anastomotic channels

to the brain. Mayer's limit of ten to fifteen minutes of cerebral anæmia, beyond which resuscitation is not practicable, is close to the correct one.

Blood, when defibrinated, soon loses its power to maintain the activity of the higher nervous centres, and its nutritive properties for all tissues quickly diminish.

Artificial fluids, as a substitute for blood, are not satisfactory.

The proper oxygenation of the blood is necessary in the resuscitation of an animal.

The heart usually continues to beat for some minutes after it ceases to affect a mercury manometer, and resuscitation of it within this period by artificial respiration alone, or combined with extrathoracic massage, or combined with extrathoracic massage and intravascular adrenalin solutions, is sometimes successful.

Resuscitation of the heart by direct massage, combined with aortic occlusion and artificial respiration, is the most certain method at our command; but for obvious reasons it is not a practical method.

Anæsthetics, hæmorrhage, and induced currents applied to the heart render resuscitation more difficult than asphyxia alone. (For References see p. 348.)

SHOCK.

In conclusion, a short account of the condition termed "surgical shock" will be given; for not only is shock of relatively frequent occurrence, but one of the grave manifestations is failure of the circulation; and methods for maintaining and restoring the circulation, of the same character as those applied in resuscitation, may be resorted to in extreme cases. Before proceeding to the detailed account of the method of treatment, a word upon the views as to the nature of shock may not be out of place. In general they are of two types; first, inhibition of the nervous centres through strong stimulation; and, secondly, exhaustion of the nervous centres due to the same cause. Both of these views have been enunciated for close on half a century, and each have their adherents. In 1864, according to Lyon and Seelig, W. W. Keen, S. Weir Mitchell, and G. R. Morehouse, enunciated practically the same theory as that put forward by Crile nearly forty years later—namely, that shock was due to vasomotor exhaustion. In 1870 Fischer published experiments which seemed to support the vasomotor exhaustion theory. In the same year Lyden expressed the view that shock was due to reflex inhibition of nerve centres. More

recently Crile published experiments which he considered as upholding a theory of vasomotor exhaustion. A little later Howell experimented with shock, and from his results he concluded that the symptoms were due primarily to alteration in the circulation, and he accounts for the circulatory state by assuming that the medullary centres presiding over the circulatory parts are thrown into a state of inhibition. He distinguishes between cardiac and vascular shock. Porter has presented experimental results that emphatically deny the correctness of the vasomotor exhaustion, and inhibition theories of experimental shock (see p. 346). Yandell Henderson in recent years published a series of papers giving experimental results and views upon shock from the standpoint of its relation to acapnia. His results from the experimental study of the effects of acapnia upon the circulation are, he states, identical with those of Ewald and Mosso. His theory of shock is very similar to Mosso's view of mountain sickness—that is, he believes that shock is due to a lack of carbon dioxide in the blood and tissues. But, so far as the writer is aware, he has not demonstrated such a carbon dioxide deficiency except in animals subjected to artificial respiration, or in which the low blood-pressure of shock was induced gradually as by exposing large surfaces, as, for example, the intestines. In other words, it has not been shown that a low carbon dioxide content of the blood is present in acute surgical shock, as in the instance of shock produced in a young man by a blow on the abdomen by the pole of a carriage, as depicted by Fischer in 1870 (see p. 343), and recently quoted by Meltzer. And, further, if such a deficit was demonstrated, it would then be necessary to show that it was not due to a decrease in its production by the tissues. And it may be further pointed out that, although tissues in an animal in a state of experimental shock show indications of stimulation after administration of carbon dioxide, this cannot be taken as indicating that the condition (shock) itself is due to the absence of this substance in the blood. Indeed, in the opinion of the writer, a more satisfactory view of the condition is that which attributes surgical shock to a general inhibitory state. Meltzer has advocated such a view, and he has not attributed the condition to circulatory inhibition phenomena alone.

Recently Lyon and Seelig have published a paper on the condition of the peripheral blood-vessels in shock. Previous to this time views were usually held that the vessels were in a state of atony. But by an ingenious experiment, which consisted in measur-

ing the flow of blood from an opening in the femoral vein in a shocked animal, they showed conclusively that upon cutting the sciatic nerve, a greater flow takes place, indicating, of course, that prior to the section of the nerve, the blood-vessels were of smaller calibre than afterwards. Indeed, their results seem to show that a

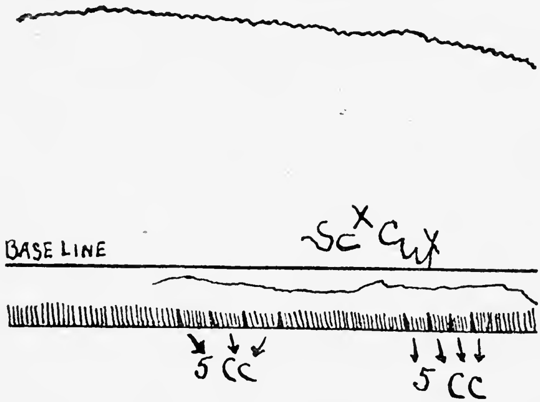


Fig. 156.—Tracing indicating Outflow of Blood from Vein in Experiment on Dog 3.

Moderate blood-pressure. No evidence of shock. Division of sciatic (at ×), followed by more rapid outflow of blood from femoral vein. Time markings, one second.

(Seelig and Lyon, *Journal of the American Medical Association*, 1909, lii. 45.)

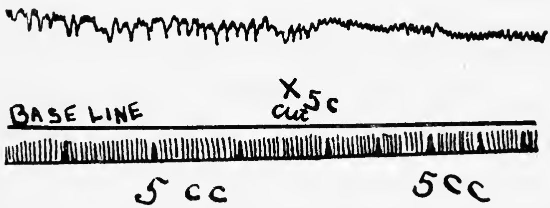


Fig. 157.—Tracing indicating Outflow of Blood in Experiment on Dog 3.

Very low blood-pressure. Animal in profound shock approaching *exitus lethalis*. Division of sciatic (×), followed by a proportionately more rapid outflow from femoral vein than in Fig. 156. Time markings, one second.

(Seelig and Lyon, *Journal of the American Medical Association*, 1909, lii. 45.)

greater dilation takes place when the sciatic nerve of a dog is cut after shock has been produced than division of the sciatic nerve of the opposite leg before shock. This result is further evidence of the inadequacy of the vasomotor theory of shock.

Crile sees a specific cause and relation between neuro-cytolytic

changes and shock, based upon the studies of Dolley, who confirmed the observations of Pike and Gomez on the chromotolitic changes in nerve cells following cerebral anæmia. The latter two writers studied materials obtained by Stewart, Pike, and the writer in the studies already described in some detail on experimental resuscitation (*cf.* p. 325). It is well known that changes of such character occur in cells of the central nervous system under a great variety of conditions—fatigue, and the administration of various drugs, such as chloroform, ether, alcohol, iodoform, etc. Therefore it is not surprising that such changes occur in animals after experimental shock. Indeed, it would be astonishing if they did not.

Numerous other views have been advanced as to the cause and nature of shock, but none of them are sufficiently supported by experimental evidence to warrant an extensive consideration in this place.

Experimentally, shock phenomena may be produced by operations which expose large surfaces and lead to actual loss of blood fluid, or to obstruction of venous return, vaso-dilation, congestion, and transudation. Therefore, Hill states that shock produced by severe injuries or operations is probably of the same nature as collapse produced by bleeding. Further, he states that in man, after a severe injury owing to the shock to the sensory synapses, there is loss of reflex tone, and relaxation of both skeletal and vascular muscle. The entire cessation of movement leads to the pooling of blood in the peripheral fields, and at the same time the injury may entail considerable loss of blood fluid. Toxic products of altered metabolism probably arise in the cooled and stagnant blood which secondarily poison the nervous system. Adrenalin and pituitary extract, by constricting the arteries, restore the blood-pressure, the former for a brief, the latter for a much longer, time.

Summing up, he states that the condition of shock or collapse is associated with cessation of the reflexes, which maintain the body in a state of vascular tone and muscular activity—hence the stagnation of the blood, fall of blood-pressure, and loss of body heat.

As Lyon and Seelig have stated, it is very important, before entering into an intimate discussion of shock, to define clearly the condition in mind, for, as Meltzer has pointed out, writers in this field have made a distinction between shock and collapse. For example, according to Meltzer, Crile states that the onset of collapse is sudden and of shock gradual; that the former condition is

amenable to stimulants, while shock is not. But it is worthy of note that Meltzer calls attention to the fact that shock as described by Crile fits only surgical shock, while traumatic shock, as described by the earlier writers, is at least chiefly of sudden onset. And the writer believes that in this connection is to be found the explanation of many of the discrepancies that appear in the writings upon the subject of surgical shock, traumatic shock, and collapse. A classical description of traumatic shock given by Fischer is typical of this class of clinical picture: "A strong and perfectly healthy young man was struck in the abdomen by the pole of a carriage drawn by runaway horses. No recognizable injury was done to any of the internal organs. Nevertheless, grave symptoms made their appearance immediately after the accident. The injured man was lying perfectly quiet, and paid no attention to anything going on around him. His face was drawn and peculiarly elongated, the forehead wrinkled and the nostrils dilated. His weary, lustreless eyes were deeply sunk in their sockets, half covered by the drooping eyelids, and surrounded by broad rings. The pupils were dilated and reacted sluggishly to light. The eyes had a glassy, vacant expression. The skin and the visible mucous membranes had a marble-like pallor. Large drops of sweat hung on the forehead and eyebrows. The rectal temperature was subnormal. The sensibility of the entire body was greatly reduced; the patient reacted slightly, and only to very painful impressions. No spontaneous movements of any sort were made by the patient. On repeated and urgent requests he showed that he could execute limited, brief movements with his extremities. When the limbs were lifted passively and then let go, they fell down as though he were dead. The sphincters were intact. The urine obtained by catheter was scanty and concentrated, but otherwise normal. The almost imperceptible pulse was rapid, irregular, and unequal. The arteries were narrow and of very low tension. The patient answered slowly, reluctantly, and only after repeated urgent questioning. His voice was hoarse and weak, but well articulated. On being repeatedly questioned, the patient complained of cold, faintness, and deadness of all parts of the body. When he shut his eyes he felt nauseated and dizzy. The respirations appeared irregular—long, abnormally deep, sighing inspirations interchanged with rapid and superficial ones, which were scarcely visible or audible."

Meltzer, recapitulating briefly the essential symptoms of this

typical case of traumatic shock, states that they consisted of general profound apathy, reduced sensibility, extreme motor weakness, great pallor, very rapid, small pulse, thready and soft arteries, irregular gasping respirations, and subnormal temperature.

The usual picture of so-called experimental shock is quite different from this in certain particulars. For example, quite properly, shock is only experimentally produced in animals that have first been reduced to a condition of complete anæsthesia. Thus the psychic phenomena are always absent. Also such shock is of gradual onset, and owing, not only to the anæsthesia, but also to the mutilation usually involved in the production of the condition, the bodily temperature is lowered before the appearance of the symptoms usually taken as an index of experimental shock, which is chiefly a lowering of the blood-pressure. Also, loss of blood and strong irritation of nerves not infrequently precedes the appearance of such symptoms. Therefore, as Porter points out, it is impossible to draw conclusions from such experiments because they confuse hydrostatic, chemical, and nervous phenomena.

The writer would lay especial emphasis upon the fact that such animals are under the influence of drugs; and that owing to lowering of body temperature, etc., the normal activities and reactions of the tissues are further altered, for it is well known to physiologists that the reactions of warm-blooded animals undergo curious alterations under such experimental conditions, so that the reactions, especially noticeable in the circulatory apparatus, assume characters more like those of cold-blooded animals. The heart of a mammal reduced to such a state will continue to beat with a much lower blood-pressure than if suddenly subjected to similar conditions. In other words, its behaviour is strikingly similar to that of a frog's heart.

It would seem, therefore, that such experimental shock may be properly called "surgical collapse"; but certainly, with present knowledge, it cannot be considered as of the same nature as traumatic shock or psychical shock. The single term "collapse" is not here employed for the reason that it is considered as being better adapted for a more general meaning. It could be better employed to indicate a clinical state presenting pronounced symptoms of approaching clinical death. It could with propriety be used for the terms traumatic and psychical shock, but since these conditions are typically of more rapid onset, and since shock

itself presents the idea of sudden force and reaction, all the terms may be employed without confusion.

Thus either traumatic, or psychical shock, or surgical collapse may result from a surgical procedure. Traumatic or psychical shock may pass into collapse. Collapse may follow hæmorrhage, suffocation, or intoxication from bacterial or other toxins, or it may occur for other reasons and in other pathological states.

Assuming that what amounts to a state of inhibition is an early condition in traumatic or psychical shock, it is interesting to sketch from the standpoint of what is known of the reactions of certain of the tissues under similar experimental conditions, an outline of some of the probable conditions and their sequence.

A case reported by Sir Astley Cooper may be taken as an extreme type: "A man walking through Fleet Street (London) one day happened to quarrel with a woman, when another man came up and gave him a blow in the region of the stomach, which caused almost instantaneous death. On dissection, no cause could be found to account for his sudden death." Here it would seem very probable that death was due to circulatory inhibition. Assuming that the blood-pressure quickly fell to, or near to, the zero-point, accounts for the clinical symptoms; for it is known that rapid and profound lowering of the arterial blood-pressure is quickly followed by disappearance of all evidences of nervous activity. Ordinarily, the heart and respiratory centre are capable of emerging from stoppage through inhibition, but it does not follow that this is invariably the case. As such inhibition is probably of a reflex character, it cannot be assumed that it lasts for an indefinite period, for the conception of such a reflex presupposes a reflex arc. And as nerve cells and connections between nerve cells and fibres (synapses) are known to be highly susceptible to anæmia, it is probable that reflex inhibition in such a case would quickly disappear. Therefore it seems probable that in the instance cited, for some unknown reason, the circulatory or respiratory mechanisms, or both, were abnormally deficient in recuperative power.

The case of the young man struck with a carriage pole differs from the last one in that the onset of symptoms which, though sudden, were less violent, is more characteristic. The picture so far as described is easily accounted for on the theory of inhibition. The same is true of psychical shock, which may present clinical symptoms identical with those in the case

just described. And from personal experience the writer can assert that the onset of psychical shock may be so rapid as to preclude the possibility of either vasomotor exhaustion—for, as Porter points out, exhaustion is always preceded by fatigue, and fatigue is a gradual process—or of acapnia as a primary factor. In fatal cases of shock it must be assumed that a stage is finally reached in which the respiratory conditions are reduced to such an extent that the higher tissues are incapable of response to reflex or direct stimulation, as with an electrical current, or to the action of drugs

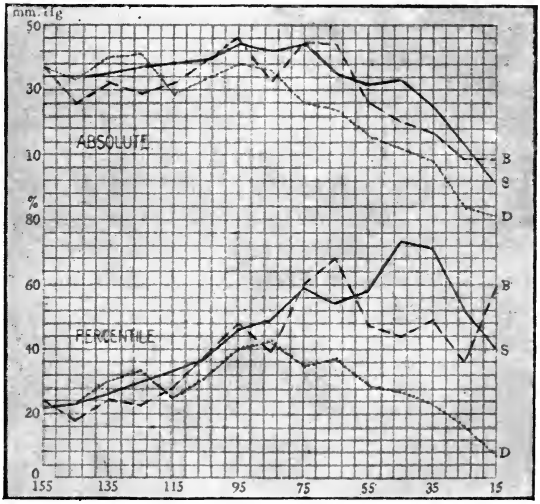


FIG. 158.—THE ABSOLUTE AND PERCENTILE CHANGE IN BLOOD-PRESSURE UPON STIMULATION OF THE CENTRAL ENDS OF THE SCIATIC (UNBROKEN LINE), BRACHIAL (LINE OF DASHES), AND DEPRESSOR NERVES (DOTTED LINE).

The abscissæ give blood-pressure in millimetres of mercury. The ordinates for the absolute curves give blood-pressure in millimetres of mercury; ordinates for the percentile curves give per cent.

(Porter, *American Journal of Physiology*, 1907-1908, xx. 404.)

(*cf.* Cerebral Anæmia). And as inhibition can only occur in tissues maintained to a certain minimum state of vitality, it is probable that such effect disappears, at least, not much later than the stage incompatible with preservation of power of response to stimulation. Illustrative of the basis of this view are Porter's observations. The percentile increase in blood-pressure in response to stimulation of the central end of a nerve, such as the sciatic, varied indirectly as the blood-pressure at the time the stimulus is applied, until the blood-pressure had fallen to a comparatively low level. In the case

of stimulation of the sciatic nerve, he states that this increase persists until the blood-pressure is 30 millimetres of mercury, which, he says, is about the level at which the spinal cord and bulbar vasomotor centre cease to respond owing to inefficient blood-supply (*cf.* p. 134).

From this conception it is easy to understand why symptoms of moderate shock, such as psychical due to thought of, or sight of, or smell of, blood, often promptly disappear after the administration of a dash of cold water or a nip of brandy or whisky, and why the treatment of different stages of shock vary so widely in the results. In general, in the opinion of the writer, after the stage is reached where shock passes into collapse, since the higher tissues by this time are in, or are at least close to, the stage of inability to respond to stimulation or to drug action, the administration of stimulating drugs which act, such as strychnine, primarily through such higher tissues, is questionable. In this stage it would seem more rational to endeavour to improve the state of the circulation by mechanical means, or by the administration of a drug, such as the constrictor principle of ergot (chrysotoxin), which, acting directly upon the muscular tissues of the blood-vessels, would theoretically, and, as shown by experiment, tend to improve the circulation, the muscular tissues being relatively resistant to anæmia, and therefore capable of responding to direct stimulation or drug action at a time when the nervous centres presiding over the circulation are in a state of oblivion. And it may be remarked that ergot has been employed thus with some success. Coupled with this, oxygen should be administered and artificial respiration given if indicated. By such means the higher tissues may be resuscitated until they are able to resume their functions adequately, if they have not suffered too profound injury.

In the treatment of shock or collapse, preceded or accompanied by severe hæmorrhage, transfusion of blood is indicated. But if the hæmorrhage has not been excessive, a subcutaneous or gradual intravenous injection of salt solution is indicated. For not only is it desirable in some such way to make up at least in part for the blood lost by hæmorrhage, but owing to the fact that it is claimed that in such conditions there is a rapid passage of liquid from the blood into the tissues, it is desirable, theoretically, to also make this loss good. Also, the introduction of salt solution into the circulation by reducing the viscosity of the blood accelerates the velocity; but caution should be exercised in order to avoid a

plethoric condition, for distension of the vascular system causes general vasomotor paralysis. And it must be remembered that salt solution introduced directly into the circulation will be quickly thrown out by the kidneys if these organs are still active. Also, it must be remembered that after a hæmorrhage the volume of blood is quickly restored to nearly normal by the entrance of liquid from the tissues into the blood-vessels. This results in thirst, and if the patient be given water the condition will be corrected in a more nearly normal manner.

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